Comparative Translational, Transcriptional, and Functional Profiling of Clear Cell and Papillary Renal Cell Carcinoma

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Written by
Certified Biologist Julia Diegmann
born 20th of February, 1977 in Fulda

Gutachter:

1. PD Dr. von Eggeling
2. Prof. Dr. Pool-Zobel
3. Prof. Dr. Hartmann

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Mit dem Wissen wächst der Zweifel.

Johann Wolfgang von Goethe

Outline

Abbreviations

aRNA	amplified ribonucleic acid
Bp	base pair
ccRCC	clear cell renal cell carcinoma
cDNA	copy desoxyribonucleic acid
CGH	comparative genomic hybridization
2D-PAGE	two-dimensional protein gel electrophoresis
DNA	desoxyribonucleic acid
IHC	immunohistochemistry
kDA	kilo dalton
mM	millimol
mTor	mammalian target of rapamycin
no.	number
PCR	polymerase chain reaction
PHA-L	phytohemagglutinin A
pRCC	papillary renal cell carcinoma
Pmol	picomol
RCC	renal cell carcinoma
rmsCD70	recombinant soluble CD70
RNA	ribonucleic acid
RT-PCR	reverse transcription-polymerase chain reaction
SAM	statistical analysis of microarrays
SELDI-TOF	surface enhanced laser desorption ionisation – time of flight
TILs	tumor-infiltrating lymphocytes
VHL	von-Hippel Lindau gene
WHO	world health organisation
µg	Microgramm

Note: Gene names are written in *italics*

1 ABSTRACT

The biology of renal cell carcinoma (RCC) remains poorly understood. RCC, which accounts for up to 3% of all adult malignancies, is the most common neoplasm in the adult kidney and has been increasing in incidence. These tumors are classified into five main subtypes: clear cell, papillary, and chromophobe RCC, as well as collecting duct carcinoma and oncocytoma. Of these, clear cell and papillary are the two most frequently diagnosed subtypes and both arise from the proximal tube of the kidney. Despite sharing a common origin, they are histologically and genetically distinguishable and thus represent an optimal model system for studying tumor-specific and tumor-subtype specific expression patterns. The aim of this study was to identify potential marker genes for clear cell and papillary RCC, assess their specificity and relevance for the tumor-subtypes, and thus contribute to a better characterization of the tumor development and behavior of RCC.

To address these questions, this study combined translational and transcriptional approaches to analyze the protein and gene expression of both tumor subtypes. The translational approach identified tumor-subtype specific protein expression patterns using SELDI-TOF technology (Surface Enhanced Laser Desorption Ionization – Time of Flight). In this way, the first specific protein pattern for papillary RCC was identified. The transcriptional approach also identified numerous genes having tumor-subtype specific regulations by using cDNA-microarrays. Genes with high potential to discriminate between normal and tumor tissue were further analyzed with independent methods. Most strikingly, the gene *CD70* was identified as being specifically over-expressed in clear cell RCC, thus revealing a new, specific marker gene. Finally, the gene expression data was bioinformatically analyzed to elucidate the underlying biology of the gene regulations found. This revealed an accumulation of apoptosis-inducing genes that are equally regulated in both RCC subtypes.

At a first glance, the induction of apoptosis seems to be antithetical to tumor survival. However, the induction of apoptosis in tumor-infiltrating lymphocytes, which are frequently observed in RCC, would provide a strategy to escape immune recognition. The group of apoptosis-inducing genes includes the gene *CD70,* which was then further studied regarding its function for the tumors in cell co-culture experiments. These experiments demonstrated the ability of CD70 to induce apoptosis in lymphocytes. Thus, *CD70* over-expression in RCC could be responsible for lymphocyte apoptosis and lymphocyte dysfunction observed within the tumor environment. This would allow for an immune suppression and as such be a new, so far unknown mechanism for RCC to escape the human immune system.

2 INTRODUCTION

2.1 EXPRESSION PROFILING AND MARKER GENE DISCOVERY

In the past decade, transcriptional and translational expression profiling became common tools for the molecular dissection of cancer as the realization took hold that cancer development and behavior could not be reduced to single gene events. This transformation in the approach to cancer research was made possible by the development of genomic and proteomic techniques like microarrays and protein chips. Initially, investigations used techniques such as array-based genotyping (Figure 1), which allows for the simultaneous assessment of many molecular markers and remains a fast, cost-effective genotyping method (1). However, this focus on the DNA level did not necessarily reveal the inner workings of the cell. Recent advances, however, now make it possible to take a closer look into the actual environment within cells by focusing on the mRNA and protein level. Nevertheless, classical approaches for expression profiling and marker gene discovery comprise either transcriptional *or* translational expression profiling. In reality though, it is important to study profile expression patterns from multiple levels in order to have a better understanding of cancer biology.

Currently, new RNA approaches applying microarray technology have been used in numerous studies to characterize various types of cancer (2-4). This approach uses the sequence resources created by the genome sequencing projects and other sequencing efforts to identify which genes are expressed in a particular cell type of an organism (Figure 1). One advantage of microarrays is the large number of genes that can be examined at the same time. However, the application of this technique in molecular studies is limited by the need for non-degraded, high quality RNAs, which are often only available in small amounts. In addition, the need for independent validation of the gene regulations found can be cost-intensive and time consuming (5). For this purpose, the majority of studies use quantitative PCR or immunohistochemistry to confirm the expression of the genes identified. Proteomic approaches have been applied recently to several types of cancer, driven by the thought that translational expression is even closer to the condition within the cells than transcriptional expression (6). In this context, SELDI-TOF (Surface Enhanced Laser Desorption Ionization – Time of Flight) technology has become a useful tool for a fast and effective profiling of the cancer proteome (7-9). Even though this technique is less expensive than microarrays, it can also be time consuming due to the need for a subsequent identification of the protein peaks found (Figure 1).

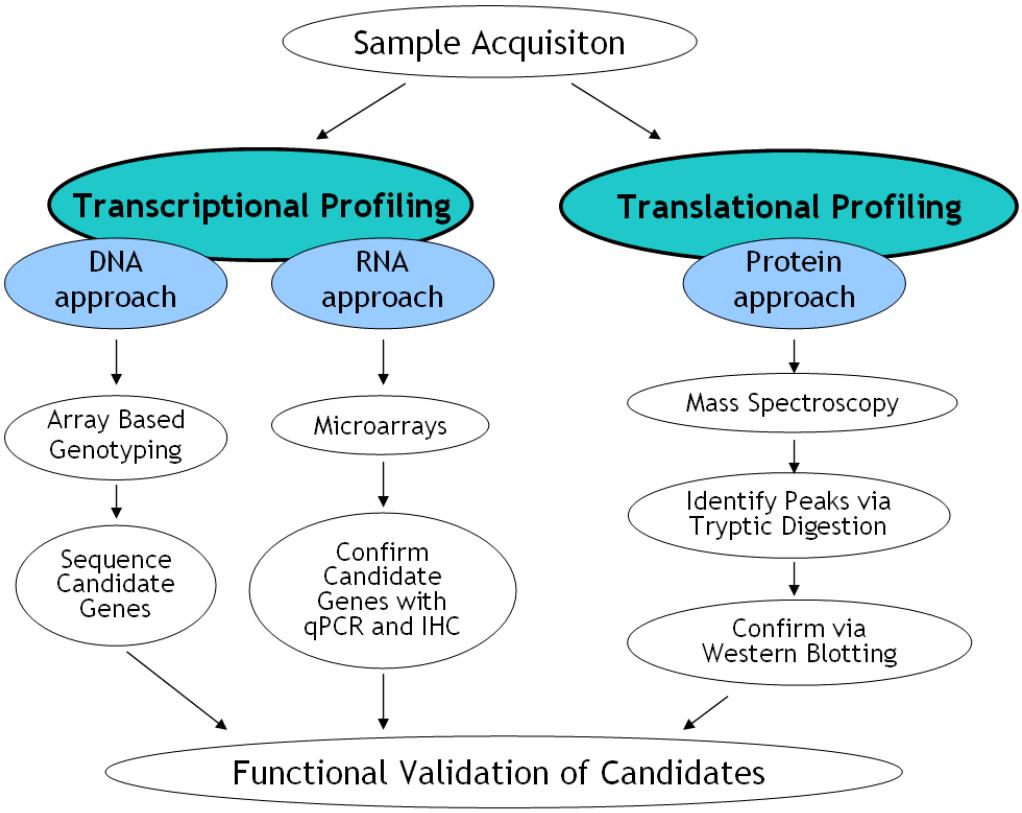


Figure 1 Overview of classical and new approaches for biomarker discovery and identification (qPCR = quantitative PCR; IHC = immunohistochemistry).

Although all approaches mentioned have been successfully applied for expression profiling and marker gene discovery in cancer (10;11), an improvement in the specificity and accuracy of profiling studies would be useful since no optimal marker gene for RCC exists and the biology of these tumors remains poorly understood (12-14). Previous studies are mostly focused on clear cell RCC and only a few took into account other RCC subtypes (15;16). Thus, this study combines the advantages of transcriptional and translational profiling by synthesizing a RNA approach and a protein approach to discover tumor-specific expression patterns for the two most common RCC subtypes, papillary and clear cell RCC. These two subtypes are an optimal model system to study the biology of RCC since they share a common cellular origin.

Gene expression studies also often suffer from simply listing gene expression data without considering their potential function within the tumor environment. Thus, in this study, the transcriptional data was additionally analyzed using a functional profiling approach. This approach searches the expression data for genes belonging to a specific pathway or common mechanism and can thus point to a biological meaning of the regulations. Comprehending the underlying expression patterns could give insights into how RCC arise and subsequently develop into different subtypes. Such a study would not only yield more potential marker genes but give insights into the biology of RCC.

2.2 Renal Cell Carcinoma

Renal cell carcinoma (RCC) comprises 3% of all human neoplasms and is increasing in incidence (17). RCC describes a family of epithelial tumors arising in the kidney that are rather homogeneous compared to other solid tumors like liver cancer, even though a variety of cell types are present. Furthermore, RCC is highly resistant to chemo-, radio-, and immunotherapy.

The molecular basis of RCC is poorly understood, with only a few relevant genes having been identified so far (chapter 2.2.2). However, several pathways associated with RCC, in particular within clear cell RCC (chapter 2.2.2), have recently been elucidated (18). These pathways include the activation of the hypoxia response pathway by mutations of the *Von Hippel-Lindau* tumor suppressor gene and activation of the mammalian target of rapamycin (mTOR) signaling pathway (chapter 2.2.2; 19;20). Finally, little is known about the immune escape mechanisms of this cancer type which, despite frequent infiltration with immune cells, successfully manages to avoid immune recognition (chapter 2.2.3).

2.2.1 Pathological Classification of Renal Cell Carcinoma

Renal cell carcinoma (RCC) can be classified based on histological appearance or solely on genetic information (Figure 2; 18). In addition to improvements in staging, appreciation for the histological diversity of RCC led to the modernization of renal tumor classification by the World Health Organization (WHO; 21). The four malignant types are clear cell, papillary, chromophobe, and collecting duct carcinoma (22;23). The clear cell variant is the most frequent type of renal cancer, accounting for approximately 70% of adult renal neoplasms, followed by the papillary variant accounting for approximately 15% (Table 1). Both clear cell and papillary RCC arise from the proximal tube.

Table 1 World Health Organization (WHO) classification of renal cell carcinoma (RCC; *21).

Benign Neoplasms	Malignant Neoplasms (*relative frequency, %)
• Renal Oncocytoma	• Clear cell RCC (~70%)
• Metanephric adenoma	• Papillary RCC (~15%)
• Papillary adenoma	• Chromophobe RCC (~5%)
	• Collecting duct carcinoma (~2%)
	• RCC, unclassified (~8%)

Several studies using classical cytogenetic analysis, comparative genomic hybridization or molecular genetic techniques showed that genetic alterations characterize the different RCC types as well as different steps of tumor development and progression (15;20;22-25). Clear cell RCC is characterized by

losses on chromosome 3p with mutations and hypermethylation of the *Von Hippel-Lindau* gene (75 %; 18). In papillary RCC, gains of chromosomes 7 and 17 are frequent (18). In chromophobe RCC, combinations of losses of chromosomes 1, 2, 10, and 13 frequently occur (Figure 2; 18).

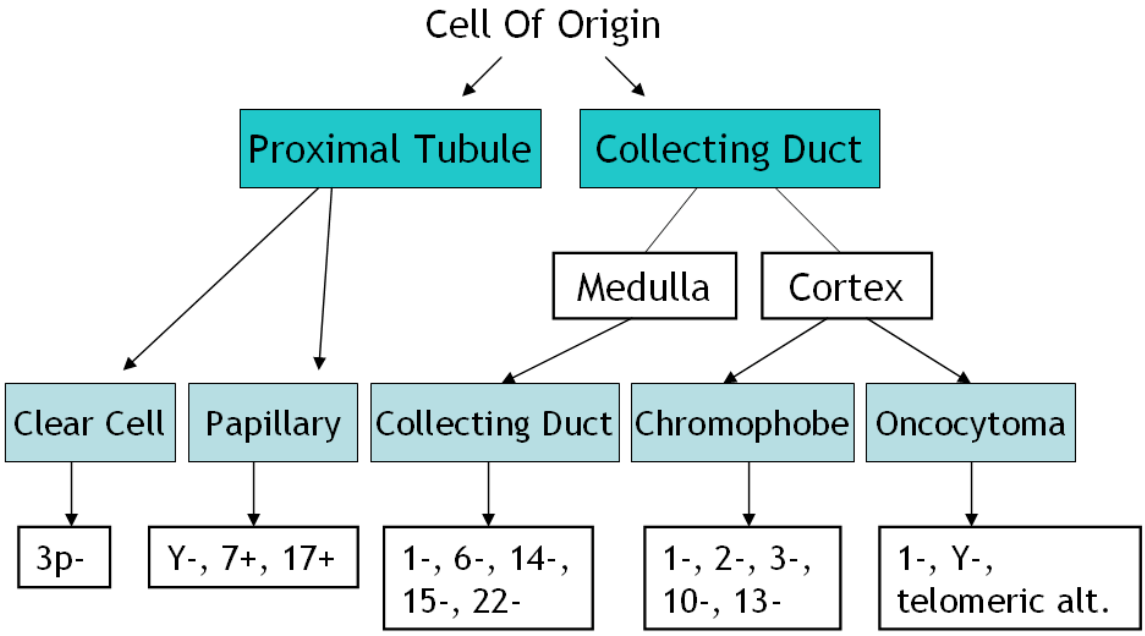


Figure 2 Current histological classification and cytogenetic correlations for renal cell carcinoma (RCC, alt. = alterations; in dark blue: cell of origin, in light blue: RCC subtype; 18).

2.2.2 Marker Genes and Pathways in Renal Cell Carcinoma

A few marker genes for renal cell carcinoma (RCC) have been identified with high-throughput technologies (14;18;26). A closer look at those genes revealed their involvement in cancer associated pathways (Table 2). For example, Ki-67 is a nuclear antigen that is selectively expressed in proliferating RCC cells (27). In RCC, *p53* mutations have been associated with cellular proliferation and a decrease in apoptosis (28). Gelsolin functions to sever actin during cell motility (29). Carbonic anhydrases (*CAIX and CAXII*) over-expression is a direct consequence of a *Von Hippel-Lindau* mutation which is found in 75% of sporadic clear cell RCC (ccRCC; 30). PTEN regulates cellular migration, proliferation, and apoptosis. EpCAM is expressed on the cell surface of most carcinomas (31). It is also known that ccRCC and papillary RCC (pRCC) express high amounts of VEGF-A, an important regulator of tumor-induced angiogenesis in RCC. Specific blocking of VEGF-A seems to lead to inhibition of tumor growth (32;33). Unfortunately, the knowledge about possible functions of these genes or proteins is limited and not confirmed by further analysis.

Table 2 Potential molecular markers and their possible function in renal cell carcinoma (18).

Function	Hypoxia inducible	Proliferation	Immune regulatory	Cell Cycle regulation	Cell Adhesion	Miscellaneous
Marker genes	CAIX CAXII CXCR-4 HIF-1α VEGF IGF-I	Ki-67 PCNA Ag-NORs	FasL IL2 IFN-gamma	p53 bcl-2 PTEN Cyclin A Akt S6 Kinase p27	EpCAM EMA E-cadherin α-Catenin Cadherin-6	Gelsolin Vimentin CA-125 CD44 Androgen receptors Caveolin-1 VEGF-R Na+/K+ ATPase subunits DNA ploidy

Some pathways enabled in RCC could be identified and the involvement of the potential marker genes was functionally elucidated. For example, the mammalian target of rapamycin (mTOR) pathway is up-regulated in RCC through the activation of downstream targets such as phosphorylated AKT (pAKT) and HIF (18). It has been speculated that not all RCC tumor types are equally amenable to treatment strategies targeting the mTOR pathway but the majority of patients have at least one component of the mTOR pathway affected (34). Another pathway, the hypoxia-inducible pathway, plays an essential role in angiogenesis, glucose transport, glycolysis, pH control, epithelial proliferation, and apoptosis of common cancers. It is known that HIF-1α and related protein HIF-2α are controlled at the post-translational level by hypoxia through the Von Hippel-Lindau (VHL) suppressor protein (35). *VHL* gene mutation or loss occurs frequently in ccRCC, suggesting a potential *VHL-HIF* tumorigenic pathway for ccRCC (36). It has been speculated that they are responsible for the ability of cancers to adapt to hypoxic environment and their resistance to radiation and chemotherapy (37;38).

Among the genes that are under the control of HIF, carbonic anhydrase (*CAIX)* is particularly important for RCC (39). *CAIX* is thought to play a role in the regulation of intracellular and extracellular pH during periods of hypoxia in tumor cells, thereby allowing cancer cells to further proliferate and metastasize (40). Previous studies have shown that *CAIX* is induced constitutively in certain tumor types but is absent in most normal tissues, with the exception of epithelial cells of the gastric mucosa (41;42). Furthermore, previous immunohistochemical studies of malignant and benign renal tissues revealed that *CAIX* was highly expressed in RCC, suggesting that *CAIX* expression may be a useful diagnostic biomarker (43;44).

The identification of these potential marker genes and enabled pathways is a crucial step towards a better understanding of the development and behavior of

RCC. However, knowledge about the mechanisms behind the ability of RCC to escape immune recognition is still very limited.

2.2.3 Immune Escape Mechanisms of Renal Cell Carcinoma

Renal cell carcinoma (RCC), like many other cancer types, has developed potent mechanisms to evade immune recognition (45). The immune system plays an important role detecting and eliminating pathogens that may do harm to the organism. Moreover, it serves as a watchdog against transformed cells that may lead to cancer (46). However, many tumors, including RCC, escape the immune system despite the presence of tumor-infiltrating lymphocytes (TILs).

Lymphocytes are the key cells of the immune system for tumor surveillance and they are part of the adaptive immune response. These cells are able to recognize numerous tumor antigens (47;48). The expression of tumor antigens may be heterogeneous within a tumor, and a single patient can develop immune reactions to multiple antigens (49). However, in many cases the immune system is not activated and ignores the tumor (50). A closer look into the immune escape strategies has revealed multiple mechanisms at the cellular and molecular level by which tumors become resistant to apoptosis or to counterattack the immune system (51). Cellular mechanisms include growing in immune privileged sites, the lack of adhesion molecules or establishing a physical barrier by stroma (52;53). At the molecular level it has been shown that tumors have impaired antigen presentation which can result in mutation or down-regulation of tumor antigens. In addition, the expression of immunosuppressive factors and molecules like cytokines or prostaglandins have been reported. Another very important strategy is the so called tolerance induction. Here, the tumors express molecules that directly influence the TILs and very often lead to their death. This strategy can explain the lack of T-cell response against tumor-associated antigens (54;55).

It is likely that RCC is able to avoid immune recognition altogether (56). Even though, like for other solid tumors, TILs have been reported for RCC, most patients appear not to generate a significant antitumor response (57). Indeed, there is little evidence for local immune reactivity within RCC, as TILs express only minimal levels of *IL-2* and *IFN-gamma* mRNAs (58;59). In contrast, there is evidence for an immune dysfunction of peripheral blood lymphocytes (60). Thus, the RCC microenvironment seems to have a deleterious effect on TILs (61). It has been hypothesized that a close interaction of lymphocytes with tumor-derived products may mediate the observed lymphocyte defect or even increased lymphocyte apoptosis within the tumor microenvironment (62). For RCC, only one mechanism for lymphocyte apoptosis has been identified so far and it is mediated by FasL (Figure 3; 62). In this mechanism, FasL binds to the receptor thus initiating the

activation of caspase 3 and 8 and leading to apoptosis. The same study also found that RCC-derived products such as gangliosides are likely to induce apoptosis in lymphocytes through inhibition of the activation of the transcription factor NF-κB even though the complete mechanism is not fully understood (62).

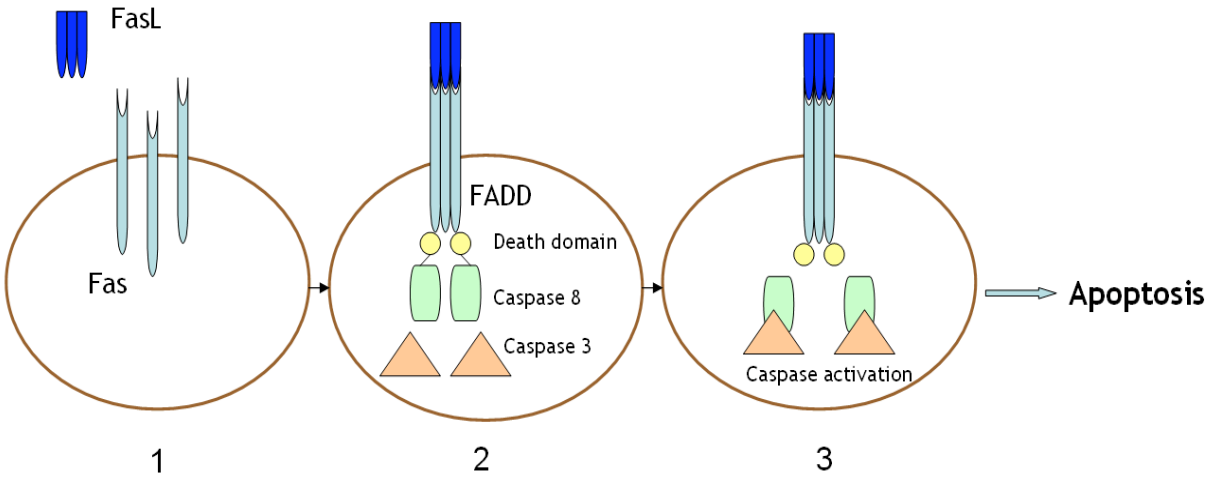


Figure 3 Schematic representation of apoptosis mediated by Fas ligand (FasL). 1. FasL is a trimeric molecule. Fas is a monomer. 2. Binding of FasL causes trimerization of Fas which then binds death domain containing adapter proteins 3. The adaptor proteins recruit and activate caspase 8 which cleaves caspase 3 and enables the apoptosis cascade (63).

3 AIMS OF THIS STUDY

The aim of this study is to provide a better understanding of the biology of renal cell carcinoma (RCC) by elucidating tumor development and tumor behavior. The tumor-specific expression patterns are to be analyzed in hopes that they might reveal the underlying biology of the regulations found and identify potential tumor-specific marker genes for clear cell and papillary RCC. Furthermore, the function of genes especially relevant for tumor development and tumor behavior shall be characterized in the course of this study.

Postulates:

1. Knowledge about the biology of RCC is still limited as is reflected by the fact that tumor development and behavior of these tumors are poorly understood.
2. RCC divides into several subtypes, among them papillary and clear cell RCC which both derive from the proximal tube. But, even though sharing a common origin, these subtypes display a unique histological and genetical pattern and are thus an optimal model system for studying tumor-specific and tumor-subtype specific expression patterns.
3. The processes which lead to cancer development are highly complex and they can not be fully explained by single gene events but by multiple changes in the expression patterns. These tumor-specific expression patterns can be detected on the translational as well as on the transcriptional level.
4. The combination of a translational and a transcriptional approach could yield a better understanding of tumor-specific and tumor-subtype specific expression patterns and lead to the identification of potential new marker genes which could thus give insights into tumor development and behavior.

Translational approach:

5. The translational approach was designed to uncover changes in protein expression of the tumor subtypes.
6. Clear cell and papillary RCC have discrete protein expression patterns that clearly separate the tumor subtypes. However, they also share protein regulations underlining their common origin. The differences in protein expression are of special interest since they can give insights into tumor behavior and tumor development.
7. For the first time, these specific protein regulations were identified for papillary RCC. Three protein peaks (3339 Da, 25595 Da, and 45888 Da) were detected with a high potential to discriminate between papillary RCC and normal renal tissue. The two most prominent proteins peaks that distinguish

between papillary and clear cell RCC have a mass of 9233 Da and 5829 Da respectively.

Transcriptional approach:

8. The transcriptional approach was designed to uncover changes in gene expression of the tumor subtypes.
9. Similar to the results from the translational approach, clear cell and papillary RCC were found to have tumor-subtype specific gene regulations but they also show similar gene expression.
10. For clear cell RCC, four genes (*FOSL2, CD70, TPA*, and *PGS2*) with a high potential to discriminate between tumor tissue and normal renal tissue could be identified. Two of these genes (*FOSL2* and *CD70*) were confirmed on the RNA level and the protein level by independent methods.
11. The gene *CD70* was identified as a tumor-specific marker gene for clear cell RCC.
12. For papillary RCC, four genes (*CD37, CALB1, MDU1,* and *CD68*) with a high potential to discriminate between tumor tissue and normal renal tissue could be identified. Three of these genes (*CALB1, MDU1*, and *CD68*) were confirmed on the RNA-level with independent methods. An additional confirmation of these molecules at the protein-level could lead to new, specific marker genes for papillary RCC.
13. The gene expression data derived from the transcriptional approach not only contains information about gene regulations but also about functional connections of the genes. Thus, a functional approach was carried out to bioinformatically search for genes that are involved in the same cellular processes.

Functional approach:

14. Several genes, which can induce apoptosis, are differentially regulated in both tumor-subtypes. Among them is the gene *CD70*.
15. In general, the induction of apoptosis seems to be antithetical to tumor behavior. But the induction of apoptosis in tumor-infiltrating lymphocytes would provide an ideal mechanism to escape immune recognition.
16. The gene *CD70,* but not its receptor *CD27* which is needed for the induction of apoptosis, is expressed by the tumor cells. In contrast *CD27* is strongly expressed by lymphocytes.
17. The ability of CD70 to induce apoptosis in lymphocytes was shown by addition of either recombinant CD70 to a lymphocyte culture or CD70 expression by RCC-cells in co-culture with lymphocytes.
18. The involvement of CD70 and CD27 in the induction of apoptosis was proven by blocking experiments with anti-CD70 and anti-CD27 antibodies.

19. The induction of apoptosis in lymphocytes via the CD70/CD27 pathway is a new, so far unknown mechanism that RCC is potentially using to escape the immune recognition.
20. The RCC subtypes, papillary and clear cell RCC, represent an ideal model system to study RCC biology since they enable the analysis of tumor-specific and tumor-subtype specific expression patterns. The synthesis of transcriptional and translational profiling represents a powerful tool for the molecular dissection of cancer. The combination of these approaches with a functional profiling also addresses functional connections between the regulations found and underlines the need for comprehensive approaches that reflect the complexity of tumor development and behavior.

4 MATERIALS AND METHODS

In order to identify potential marker genes, expression profiling in clear cell and papillary renal cell carcinoma (ccRCC and pRCC) was performed on the genomic and proteomic level. For the protein expression profiling, a total of 40 RCC tissue samples (20 pRCC and 20 ccRCC) were analyzed via translational profiling (Part A of Figure 4 and chapter 4.3.1). To elucidate the gene expression patterns a total of 16 RCC tissue samples (10 ccRCC and 6 pRCC) were subjected to a transcriptional expression analysis (Part B of Figure 4 and chapter 4.3.2). The genes found were analyzed via functional profiling (Part C of Figure 4 and chapter 4.3.3) and one specific gene, *CD70*, was examined more closely regarding its role within the tumor environment (Part D of Figure 4 and chapter 4.3.4).

4.1 STRUCTURAL OVERVIEW OF EXPERIMENTS

For the expression profiling, two different approaches were applied (Figure 4). First, the protein expression was examined via SELDI-TOF (Surface Enhanced Laser Desorption Ionization – Time of Flight) technology creating specific protein expression patterns for each tumor-subtype. Second, gene expression was analyzed via cDNA-microarrays resulting in lists of differentially expressed genes specific for both tumor-subtypes.

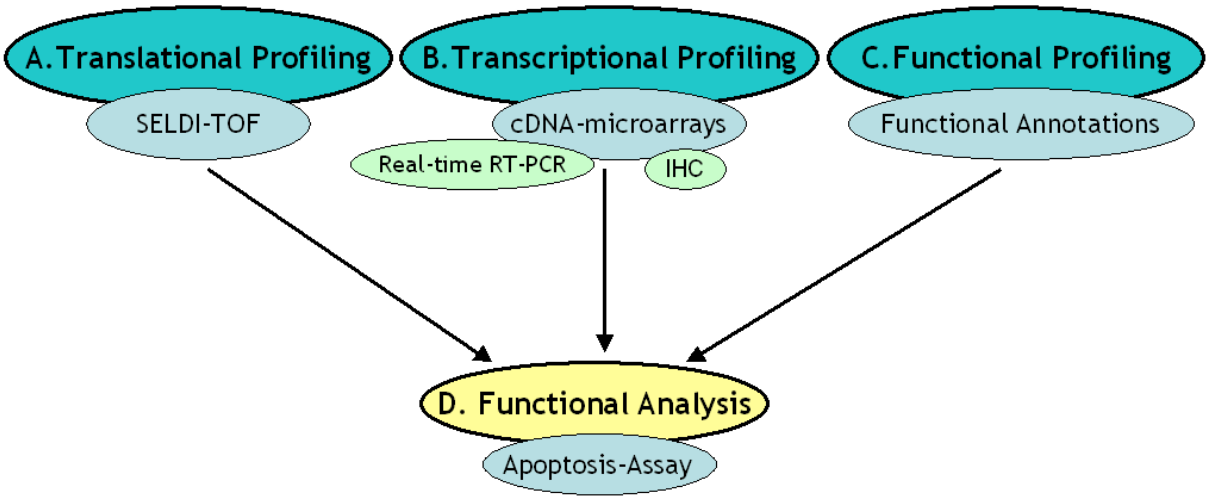


Figure 4 Structural overview of experiments. (In blue bubbles: the profiling approaches used for target molecule identification, in light blue bubbles: the technical realization of the approaches, in light green bubbles: the confirmation methods for the gene expression data, in yellow bubble: the functional characterization of target molecule).

For selected genes, a confirmation step was carried out using quantitative PCR (qPCR) as well as immunohistochemistry (IHC). Third, functional profiling was done in order to compare the gene expression datasets elucidating underlying patterns, like regulated genes that are involved in the same processes. Fourth, a functional analysis of one specific gene of interest was carried out using cell culture models

for apoptosis studies via an Apoptosis Assay (Figure 4). A description of the sample types used for these analyses is given in chapter 4.2, a detailed explanation about the methods used for the realization of the described approaches can be found in chapter 4.3.

4.2 MATERIALS

The experiments were carried out with two different sample types: for the profiling approaches tissue samples from clear cell renal cell carcinoma and papillary renal cell carcinoma (ccRCC and pRCC) were used. For the functional analysis RCC cell lines, a T-lymphocyte cell line, and native lymphocytes isolated from peripheral blood were used.

4.2.1 TISSUE SAMPLES

Samples from 30 patients with ccRCC and 26 patients with pRCC, containing non-tumorous ("normal") and tumor tissue were obtained from fresh nephrectomy specimens (Table 3). The samples were snap frozen in liquid nitrogen and stored at –80°C at the Department of Urology of the Friedrich-Schiller-University, Jena. Paraffin sections from each specimen were reviewed by a pathologist and classified histologically according to UICC-TNM classification (1997). All Fuhrmann grading spectra (1-3) are represented (Table 3). Additionally, for all patient samples the histological classification was confirmed with a CGH-Analysis (Appendix I) that verified all 56 cases. A total of ten ccRCC samples and six pRCC samples were analyzed with cDNA-microarrays whereas 20 ccRCC samples and 20 pRCC samples were analyzed with SELDI-TOF technology (Table 3).

For the immunohistochemistry experiments carried out at the department of Urology a total of 68 tumor samples were analyzed, including 41 ccRCC (which includes those that were also analyzed via microarray and qPCR), 19 pRCC (which includes those that were also analyzed via microarray and qPCR), five chromophobe RCC, and three oncocytomas.

Table 3 Overview of patient samples. A Papillary renal cell carcinoma B. Clear cell renal cell carcinoma (pT= extension of primary tumor, pN=infiltration of lymphnodes, pM=metastasis)

pTX: Primary tumor cannot be assessed, pT0: No evidence of primary tumor, pT1: Tumor 7 cm or less, limited to kidney,pT2: Tumor greater than 7 cm, limited to kidney, pT3: Tumor extends into major veins/adrenal/ perinephric tissue; not beyond Gerota's fascia, pT3a: Tumor invades adrenal/perinephric fat, pT3b: Tumor extends into renal vein(s) or vena cava below diaphragm, pT3c: Tumor extends into vena cava above diaphragm, pT4: Tumor invades beyond Gerota's fascia; pN - Regional lymph nodes, pNX: Regional nodes cannot be assessed, pN0: No regional lymph node metastasis, pN1: Metastasis in a single regional lymph node, pN2: Metastasis in more than one regional lymph node, pM - Distant metastasis, pMX: Distant metastasis cannot be assessed, pM0: No distant metastasis, pM1: Distant metastasis.

A. Clear cell renal cell carcinoma

Patient	Appearance	Grading	pT: extension of primary tumor	pN: infiltration of lymph nodes	pM: metastasis	Analysis
1	Tubulary	-	1	-	-	cDNA-array
2	Azinary, tubulary	2	-	-	-	cDNA-array
3	-	2	3b	0	-	cDNA-array
4	Azinary, tubulary	2	-	-	-	cDNA-array
5	solid, compact, tubulary	2	3a	0	x	cDNA-array
6	Solid	3	-	-	-	cDNA-array
7	Azinary, tubulary	2	-	-	-	cDNA-array
8	Trabeculary	2	-	-	-	cDNA-array
9	Azinary, tubulary	2	-	-	-	cDNA-array
10	-	2	-	-	-	cDNA-array
11	Aleveolary	1	-	-	-	cDNA-array
12	Tubulo-azinary	2	1	0	-	SELDI-TOF
13	Azinary, trabeculary	2	-	-	-	SELDI-TOF
14	Solid, tubulo-papillary	2	2	0	x	SELDI-TOF
15	-	2	3a	0	0	SELDI-TOF
16	Trabeculary, azinary	2	2	0	x	SELDI-TOF
17	Solid, azinary	1	3b	0	x	SELDI-TOF
18	Solid	2	2	2	x	SELDI-TOF
19	Azinary, trabeculary	1	1	-	-	SELDI-TOF
20	Compact	2	3a	1	x	SELDI-TOF
21	Solid, azinary	1	3b	0	x	SELDI-TOF
22	-	2	1	0	x	SELDI-TOF
23	Trabeculary, azinary	2	2	0	x	SELDI-TOF
24	Solid, compact	2	2	X	x	SELDI-TOF
25	Compact, trabeculary	2	1	0	x	SELDI-TOF
26	Comact, zystical	2	1b	X	1	SELDI-TOF
27	Solid	-	3a	0	x	SELDI-TOF
28	Complex	3	3b	-	-	SELDI-TOF
29	Compact	2	2	X	x	SELDI-TOF
30	Trabeculary	2	4	0	x	SELDI-TOF

B. Papillary renal cell carcinoma

Patient	Appearance	Grading	pT: extension of primary tumor	pN: infiltration of lymph nodes	pM:metastasis	Analysis
1	Papillary	2	1a	-	-	cDNA-array
2	Papillary	3	1	0	-	cDNA-array
3	Papillary	2	1b	0	X	cDNA-array
4	Tubulo-papillary	-	1	-	-	cDNA-array
5	Papillary	-	3a	-	-	cDNA-array
6	Tubulo-papillary	1	3a	0	X	cDNA-array
7	Papillary	-	1b	-	-	SELDI-TOF
8	Tubulo-papillary, solid	3	2	1	x	SELDI-TOF
9	Papillary	-	3a	-	-	SELDI-TOF
10	Papillary	1	1a	0	x	SELDI-TOF
11	Papillary	-	1	-	-	SELDI-TOF
12	Papillary	2	1a	x	x	SELDI-TOF
13	Papillary	-	2	-	-	SELDI-TOF
14	Papillary	-	-	-	-	SELDI-TOF
15	Papillary	2	2	x	x	SELDI-TOF
16	Tubulo-papillary	2	-	-	-	SELDI-TOF
17	Papillary	2	1	x	x	SELDI-TOF
18	Tubulo-papillary, alveolary	2	2	0	x	SELDI-TOF
19	Tubulo-papillary	2	-	0	x	SELDI-TOF
20	Tubulo-papillary	2	2	0	x	SELDI-TOF
21	Tubulo-papillary	2	1	0	x	SELDI-TOF
22	Papillary, solid	2	2	0	x	SELDI-TOF
23	Papillary	2	-	-	-	SELDI-TOF
24	Tubulo-papillary	2	2	-	-	SELDI-TOF
25	Solid, Trabeculary	2	-	-	-	SELDI-TOF
26	Solid, Compact	1	1 (3)	0	x	SELDI-TOF

4.2.2 Cell Lines and Native Lymphocytes

For the functional analysis three RCC cell lines, one T-lymphocyte cell line as well as primary lymphocytes isolated from peripheral blood were used. A description of the established RCC cell lines, A498, CAKI1, CAKI2, and MOLT-4 and their cell culture conditions is given in Table 4. The cells were cultured at 37°C and 5% CO_2.

Table 4 Overview of cell lines used for cell culture experiments.

Cell Line	Cell Type	Growth Conditions	Growth Properties
CAKI1	Human Kidney Carcinoma	DMEM + 10% FCS	Adherent
CAKI2	Human Kidney Carcinoma	DMEM + 10% FCS	Adherent
A498	Human Kidney Carcinoma	RPMI + 10% FCS	Adherent
MOLT 4	T-Lymphocytes	RPMI + 10% FCS	Suspension

Lymphocytes were isolated from peripheral blood with lymphocyte separation medium according to manufacturer's instructions. Stimulation of lymphocytes was carried out by adding 12 µg/ml phytohemagglutinin A (PHA-L). The cells were cultured at 37°C and 5% CO_2. Lymphocytes were cultivated 72 h before adding 50 ng/ml recombinant soluble CD70 (rmsCD70) to the cell culture.

4.3 Methods

4.3.1 Translational Profiling

For the translational approach a total of 20 clear cell and 20 papillary renal cell carcinoma tissue samples were used. This analysis was done to profile the protein patterns of both tumor-subtypes. The profiling was carried out using SELDI-TOF protein chips. Before applying the sample to the protein chip a cell lysis and protein extraction as well as a protein chip preparation was performed (chapter 4.3.1.1).

4.3.1.1 SELDI-TOF

Cell Lysis and Protein Extraction. The cells were lysed using a specially developed lysis buffer (Buffer D; 64). Approximately 0.5 mg of frozen tissue was cut into slices in a cryostat in order to mechanically disrupt the cell membranes. Buffer D (200 µl) was placed immediately onto the slices. Samples were incubated on ice for 30 min and then centrifuged at 15000 rpm at 4°C for 15 min. The supernatant was used for subsequent protein chip analyses.

Buffer D

0.1 M Na-Phosphat
5 mM EDTA
2 mM $MgCl_2$
3 mM β - 2 – Mercaptoethanol
freshly added:
1% CHAPS
500 µM Leupeptin
0.1 mM PMSF

PROTEINCHIP ARRAY PREPARATION AND ANALYSIS. The extracted proteins from ccRCC and pRCC tissues were analyzed on a strong anion exchange array with quaternary amine functionality (Q10). The protein binding to the array was performed using a bioprocessor. First, array spots were equilibrated three times by applying 150 µl binding/washing buffer for 5 min at room temperature with vigorous shaking. After equilibration, samples were immediately applied to the spots (100 µg per spot) diluted in binding buffer and incubated with vigorous shaking for 30 min at room temperature. After removal of the samples, each well was washed three times with 150 µl binding/washing buffer, followed by washing them twice with 150 µl water to remove the buffer salts and the samples were subsequently allowed to airdry. After two applications of 1 µl saturated sinapinic acid, mass analysis was performed in a ProteinChip System 4000 Series (PCS 4000 TOF – MS Personal) according to an automated data collection protocol. This includes an average of 195 laser shots to each spot with a laser intensity of 200 µA and 270 µA, respectively, depending on the measured region (low: 2–20 kDa and high: 20–200 kDa, respectively). The detector sensitivity was 9. Normalization of all spectra was performed using total ion current.

Binding/washing buffer

100 mM Tris Buffer (pH 8.5)
0.05% Triton x-100

Saturated Sinapic Acid

dissolved in
50% Acetonitrile
0.5% Trifluoroacetic acid

4.3.1.2 BIOINFORMATICAL ANALYSIS OF SELDI-DATA

The bioinformatical analysis was done with two methods based on different statistical evaluations. First, the biomarker wizard software was used for calculation of p-values based on the Mann-Whitney U test for non-parametric data sets (65). Second, the program XL-miner, a cluster and rule-based data mining algorithm, was used to find specific protein sets that distinguish between the classifications (66).

NORMALIZATION. Normalization of the protein expression was based on two assumptions. First, the average protein expression should be the same for all

samples and second, differences are due to sample preparation or handling. Therefore the average protein expression of each sample was calculated and subtracted from every expression value of that particular sample. Since a Lilliefors test showed that the data were rather log-normal than normal distributed all expression values were log_2-transformed prior to this normalization procedure.

SOFTWARE AIDED DATA INTERPRETATION WITH BIOMARKER WIZARD. Data interpretation was performed with the ProteinChip Software (version 3.0) to summarize generated protein profiles of all normal and tumor tissues. Cluster analysis of the detected signals and the determination of respective p-values were carried out with the Biomarker Wizard Program (Version 3.0; Ciphergen Biosystems Inc., Fremont CA). For p-value calculation, spectra with at least 10 signals in the range between 2 kDa and 20 kDa exhibiting a signal noise-to-ratio (S/N) of at least 5 were selected and analyzed with the Mann-Whitney U test for non-parametric data sets (65).

SOFTWARE AIDED DATA INTERPRETATION WITH XL-MINER. Statistical analysis of the differentially expressed proteins was performed with the Software XL-miner. This program is a cluster and rule-based data mining algorithm (66). The CE software was used for the processing of raw spectra and the calculation of *p*-value and cluster plots according to the manufacturer's instruction. This cluster and rule based data mining method consists of a clustering algorithm , a rule extraction and rating step and a rule base construction step (67). All these steps are supervised with respect to the given sample classification (e.g. tumor versus normal tissue). Additionally the data were normalized in a pre-processing step.
First, the pre-processed protein expressions were clustered into two clusters – "low expressed" and "high expressed" – for each peak. Clusters were generated automatically using a supervised fuzzy clustering algorithm (68). For this purpose the median expressions of the given sample classes (e.g. the two classes: normal samples and tumor samples) were taken as the cluster borders. All samples with expression values below the lowest border were assigned to cluster "low expressed" with a membership of 1 and accordingly all samples with expression values above the highest border were assigned to cluster "high expressed" with a membership of 1.
Second, the rule extraction and rating was carried out to find those features (peaks) with the most similar membership distribution compared to the given sample class distribution. For this purpose, "rules" are generated. Such rules consist of a condition part that is formed by one of the generated clusters and a conclusion part that is formed by one of the given sample classes. They can be written in the form: IF patient belongs to cluster '*peak X high expressed*' THEN

patient belongs to class '*tumor*'. Combining all generated clusters and all given sample classes leads to a complete set of uni-conditional rules. These rules are logical hypotheses that have to be rated to find whether they are true or not. In this work the rules were rated using a statistically based rule rating measure introduced by Kiendl and Krabs that assesses the difference between the probability for the conclusion in the whole data set and the probability for the conclusion under the respective condition (69). Rules with a rule rating measure greater than zero were then ranked in a rule list.
Third, with the rule base construction a small subset of rules is found which forms a rule-base that is used for automatic classification of new patient samples. A rule-base contains at least one rule for every possible classification outcome. To classify a new patient sample the cluster memberships (condition part of the rules) of all rules out of the rule base that point to the same classification outcome (conclusion part of the rules) are added and the sample is assigned to the class with the highest sum. To construct a rule base that gives a good representation of the data set investigated all combinations of rules were permuted and the rule base with the smallest classification error and the smallest number of rules was chosen. The rules included in the chosen rule base represent markers that can distinguish between the sample classes under investigation. This rule base serves as a basis for the calculation of sensitivity (true positives / (true positives + false negatives) and specificity (true negatives / (true negatives + false positives) of the found rules.

4.3.2 TRANSCRIPTIONAL PROFILING

Transcriptional profiling is a method used for monitoring gene expression by measuring the amounts of transcribed mRNAs. This is possible due to rapid advances in high-throughput measurement technologies, like cDNA-microarrays. Here, transcriptional profiling was performed on clear cell and papillary renal cell carcinoma (ccRCC and pRCC) with pre-designed PIQOR™ microarrays (Miltenyi Biotec GmbH). First, the total RNA was extracted from the tissue followed by an amplification of the mRNA (chapter 4.3.2.1). The hybridization, scanning, and evaluation of the microarrays was carried out according to Miltenyi Biotec´s standard protocol (chapter 4.3.2.1). A confirmation of the found regulations was done on the RNomic level using quantitative PCR (qPCR) and on the proteomic level using immunohistochemistry (IHC; chapter 4.3.2.2).

4.3.2.1 cDNA-MICROARRAYS

TOTAL RNA EXTRACTION. Approximately 2-4 mg tissue was used for each RNA extraction. Samples were reduced to small slices by cutting the frozen tissue with a

cryostat. Total RNA was isolated by standard methods using the commercially available RNeasy RNA Isolation Kit. Qualitative integrity test of purified total RNA was done by capillary electrophoresis using a Bioanalyzer 2100. The amount of RNA was measured with an UV-spectrophotometer. Only those samples that showed no RNA degradation were further analyzed.

LINEAR AMPLIFICATION OF RNA. Linear amplification of RNA was done using a previously developed method (70). For the first strand synthesis 2 µg total RNA was added to the First Strand Mix. The mixture was incubated at 65°C for 5 min and cooled down to 42°C before adding 2 µl SSII RT (400 U). The samples were incubated again at 42°C for 1 h and put on ice. For the second strand synthesis, all reagents and tubes had to be ice cold. All components of the Second Strand Mix were added and samples were incubated at 16°C for 2 h. For the clean-up of dscDNA QIAquick was used according to the manufacturer's protocol. After the clean-up, samples were dried in a speed vac and resuspended in 8 µl RNase-free H_2O.

First Strand Mix
4 µl 5 x First Strand Buffer
2 µl 0.1 M DTT
1 µl 100 pmol/µl T7-(T)24 primer
1 µl 10 mM dNTPs

Second Strand Mix
30 µl 5 x Second Strand Buffer
4 µl DNA Polymerase I (40 U)
3 µl 10 mM dNTPs
1 µl E. coli DNA Ligase (10 U)
0.7 µl RNase H (2 U)
91.3 µl DEPC H_2O

For the amplified RNA (aRNA) synthesis a Megascript T7 in vitro transcription Kit was used. All reagents had to be at room temperature. A NTP Mix was prepared and added to the samples together with 2 µl Enzyme Mix. The mixture was incubated in a thermocycler at 37°C for 6 h.

NTP mix (per tube)
2 µl ATP solution (75 mM)
2 µl GTP solution (75 mM)
2 µl CTP solution (75 mM)
2 µl UTP solution (75 mM)
2 µl 10 x Reaction Buffer

The samples were cleaned again using a RNeasy Kit according to manufacturer's instructions. Samples were now labeled to generate fluorescently labeled first strand cDNA. A total of 2 µg aRNA was used for the labeling reaction. Control RNA 1, Control RNA 2, and (10x) Hexanucleotide Mix (each 2 µl) were added to the samples. aRNA samples were quantified by spectrophotometry and quality was assessed again by capillary electrophoresis (Bioanalyzer 2001). Again only those samples that showed no degradation and with an average length of 300 bp per aRNA were further analyzed.

TYPES OF MICROARRAYS. For the microarray experiments two different types of arrays were used. The aRNAs derived from ccRCC were hybridized on the PIQOR™ Immuno/Onco Array (642 cDNA probes) whereas the aRNAs derived from pRCC were hybridized on the PIQOR™ Immunology microarray (1070 cDNA probes; Figure 5).

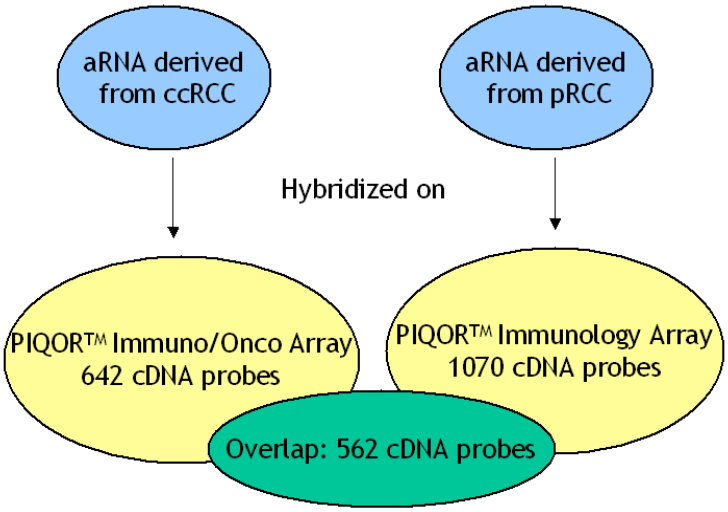


Figure 5 Overview of cDNA – array types used for the experiments (aRNA = amplified RNA, ccRCC = clear cell renal cell carcinoma, pRCC = papillary renal cell carcinoma).

Both microarrays contain genes belonging to the categories listed in Table 5. The overlap between these different microarrays exhibits 562 cDNA probes.

Table 5 Gene categories present on the used microarrays (n.s.: not specified).

Gene Category	Details
Apoptosis, signal transduction, stress	caspases, MAP-kinases, TRAFs, BCL-family, HSP70- family death domain containing proteins, tyrosine protein kinases, pi3-kinases
CD antigens	n.s
Cell cycle, DNA-repair	cyclins, BRCA-family, P53, P73, DNA-Ligases
Chemokine receptors	n.s
Chemokines	n.s
Complement system	n.s
Cytokines	interleukines, TGFA/B, PDGFA/B, TNFα and other members of the TNF-family, IFNg, BMPs, inhibins, TGFß-family
Cytokine receptors	interleukin receptors, TNF receptors
Cytokine signaling and regulation	JAK/STAT, SOCS, IRAK, NFAT
Extracellular matrix proteins	collagens, matrix-metalloproteases, TIMPs, matrillins, integrins, laminins, thrombospondins
Inflammation	NFkB metabolism, TOLL-receptors, phospholipases A2, prostaglandin receptors

HYBRIDIZATION OF MICROARRAYS. Hybridization of ImmunoOnco PIQOR™ and Immunology PIQOR™ slides was performed according to manufacturer's guidelines using a GeneTAC hybridization station and hybridization chamber respectively. The aRNAs (2 μg) from normal and tumor tissue were reverse-transcribed by adding a labelling mix. Samples were then incubated at 42°C for 30 min. After addition of

1 µl of SuperScript™ II Reverse Transcriptase samples were incubated again at 42°C for 30 min. RNaseH (0.5 µl) was added and the samples were incubated at 37°C for 20 min to hydrolyze RNA.

Labeling Mix
8 µl 5x First Strand Buffer
2 µl Primer-Mix
2 µl low C-dNTPs (10 mM dATP, 10 mM dGTP, 10 mM dTTP, 4 mM dCTP)
2 µl FluoroLink Cy3/5-dCTP respectively
4 µl 0.1 M DTT
1 µl RNasin (20 to 40 U)
200 U of SuperScript™ II Reverse Transcriptase

Cy3- and Cy5-labeled samples were combined and cleaned using QIAquick™. Eluents were diluted to a volume of 50 µl. Hybridization solution (2x; 50µl), pre-warmed to 42°C, was added to the labeled samples.
To prepare the slides for hybridization, 100 µl of prehybridization solution were pipetted onto the slides which were then prehybridized at 65°C for 30 min. Thereafter, 100 µl purified Cy3- and Cy5-labeled probes in hybridization solution (2x) were pipetted onto the slides thereby displacing the prehybridization solution. Hybridization was performed for 14 h at 65°C, followed by four washing steps carried out at 50°C (71).
Image capture of cDNA arrays was done with a laser scanner (ScanArray 4000 Lite or GenePix 4000B respectively). ImaGene software version 4.1 was used for signal quantification. The signal was measured for each spot inside a circle adjusted to the individual spot (160 – 230 µm diameters). Background was measured outside the circle within specified rings 30 µm distant to the signal and 100 µm wide. Signal and background were taken as the average of pixels between defined low and high percentages of maximum intensity defined as 0/97% for signal and 2/97% for background. Local background was subtracted from the signal to obtain the net signal intensity for both fluorescent dyes, Cy5/Cy3. First, the ratio was computed with the intensities for both dyes. Second, the mean of ratios of two corresponding spots representing the same cDNA was computed. The mean ratios were then normalised to the median of all mean ratios. This was done by using only those spots with a fluorescent intensity in one of the two channels that was two times above the negative control. The negative control for each array was computed as the mean of the signal intensity of two spots representing herring sperm RNA and two spots representing spotting buffer only. Only genes displaying a net signal intensity two-fold higher than the negative controls in the control sample or treatment sample were used for further analysis. Normalized ratios are shown as Cy5 signal intensity divided by Cy3 signal intensity of the respective gene. Unsupervised cluster analysis (Average Linkage Clustering) was carried out using

"Cluster" and "Tree View" programs according to Eisen (72). All microarray experiments were performed according to the MIAME guidelines (73).

4.3.2.2 CONFIRMATION OF TRANSCRIPTIONAL PROFILING

To verify the gene expression data obtained by cDNA-microarrays two independent methods were used. On the RNomic level a quantitative PCR (qPCR) was performed. On the protein level immunohistochemistry (IHC) for selected proteins was carried out.

QUANTITATIVE PCR. To confirm the clear cell RCC gene expression data two gene primer pairs for *CD70* and *FOSL2* as well as one reference gene primer pair for *MCP* (Table 6) were designed from the published sequence of human SCC (SCC A1: DDBJ/EMBL/GenBank; HSU19556) antigen cDNA. The selection criteria for the corresponding amplified cDNA fragment include homology to other known genes (85%) and uniformity of the fragment length. All selection criteria are summarized in detail elsewhere (73). The primer design was performed with the software OLIGO (version 5.0).

Table 6 Primer sequences for quantitative PCR to confirm gene expression data (tm = melting temperature).

Candidate genes	Sense primer 5´-3	Antisense primer 5´- 3´	Tm (°C)
CD70: Tumour necrosis factor ligand) superfamily, member 7	AATCACACAGGACCTCAGCAGGACC	AGCAGATGGCCAGCGTCACC	88,8
FOSL2: FOS-related antigen 2	CCCTGCACACCCCCATCGTG	TGATTGGTCCCCGCTGCTACTGCTT	89,8
MCP: Membrane cofactor protein	ACTACAAAATCTCCAGCGTCCAG	CAACTATGGCAATAACAATCACAGC	82,2

Specificity of the desired qPCR products was documented using gel electrophoresis and melting curve analysis (LightCyler Software Version 3.5, 2001, Roche Molecular Biochemicals). The product specific melting curves showed only single peaks and no primer dimer peaks or artefacts.

To confirm the papillary RCC gene expression data four primer pairs for the genes *CALB1, CD98, CD68*, and *CD37* as well as one reference gene primer pair for *IL1RAP* were purchased from Qiagen (QuantiTect Primer assay). These primer pairs were specifically designed and developed for qPCR (Light Cycler).

The following steps were carried out for all primer pairs equally. The aRNAs (2 μg) from both tumor and normal tissue were reverse transcribed with SuperScript™II Reverse Transcriptase using 100 μM random hexamer primers according to the manufacturer's protocol. Experiments were performed with a LightCycler in capillaries using a Quantitect SYBR Green master mix containing HotStartTaq DNA

polymerase and SYBR-Green I deoxyribonucleoside triphosphates used according to manufacturer's instructions. The following qPCR protocol was applied for all genes:

- initial denaturation program for activating the HotStart enzyme (15 min at 95°C)
- amplification and quantification program repeated 45 times (15s at 95°C; 10s at 55°C; 30s at 72°C) with a single fluorescence measurement.

After completion of PCR amplification, a melting curve analysis was carried out. The *"delta-delta CT method"* for comparing relative expression results in qPCR was applied (74).

IMMUNOHISTOCHEMISTRY. Immunohistochemistry was performed on frozen sections (8 µm) or cells grown in 96-well plates respectively which were fixed in acetone for 10 min. Washing of slides was performed with Tris Buffer/Tween (0.1% w/v Tween, TBS-T) for 5 min. Slides were overlaid with 0.1% avidin for 10–15 min followed by an overlay with 0.01% biotin for 10–15 min. Biotin blocking was performed using the biotin blocking system from DAKO. After washing with TBS-T twice for 1 min and incubation for 10 min, protein blocking was carried out using a blocking solution containing 25 ml serum from goat in 250 ml TBS, 25 ml RPMI 1640, and 250 mg sodium azide for 10 min. The slides were washed three times for 1 min and incubated for 10 min with TBS-T. The primary antibody-antigen reaction was performed with the primary antibody (CD70, CD27, FOSl2, CD37, and CXCR4; dilution 1:250 for CD70 and FOSL2, 1:200 for CD27, CD37 and CXCR4) overnight at 4-8°C. After washing with TBS-T (for 3x1 min and 1x10 min), slides were incubated with the biotin coupled secondary antibody (DAKO kit 5005) for 35 min according to manufacturer's instructions. Slides were washed again with TBS-T (3x1 min, 1x10 min) and Avidin-alkaline-phoshatase (DAKO kit 5005) solution was added for 30 min. After washing with TBS-T (3x1 min, 1x10 min), the enzyme reaction was carried out adding substrate (DAKO kit 5005) solution for 7 min. Slides were washed with water (3x1 min, 1x10 min). Finally, sections were stained with Haemalaun solution.

TBS

50 mM Tris
150 mM NaCl
H_20/1L

TBS-T

50 mM Tris
150 mM NaCl
1 % Tween 20
H_20/1L

4.3.3 FUNCTIONAL PROFILING

In order to compare the two cDNA-microarray gene expression datasets for clear cell renal cell carcinoma and papillary renal cell carcinoma (ccRCC and pRCC), a functional profiling was performed. Both tumor-subtypes were searched for equally and differentially expressed genes which were then subjected to a functional

annotation analysis. This method identifies enrichments of genes belonging to a common pathway or sharing other biological properties.

4.3.3.1 Gene Expression Data Preprocessing and Clustering Analysis

As the datasets for ccRCC and pRCC gene expression were generated by using different topic-defined microarrays, the analysis has been restricted to the subset of 562 PIQOR™ probes present on both microarrays (Figure 5). For statistical analysis of the microarray data the software SAM (Statistical Analysis of Microarrays) was used (75). First, genes with missing values in the majority of experiments (>60%) were discarded. Second, any missing values in the remaining genes were estimated by 'N-nearest neighbor imputation' (76). This analysis resulted in two datasets: one containing all genes that are up- or down-regulated in both tumor-subtypes (subsequently called “equally regulated genes”) and a second one containing genes that are differentially expressed between the tumor-subtypes. A functional annotation analysis for those datasets was performed by screening each dataset for a significant enrichment of genes belonging to a common pathway or sharing other biological properties.

4.3.3.2 Functional Annotation Analysis

Both datasets, for equally and differentially regulated genes in both tumor-subtypes, were subjected to a pathway annotation analysis using Miltenyi´s TreeRanker system (Miltenyi Biotec GmbH). This software system analyzes groups of genes for a statistically significant enrichment of biological pathway annotation terms. These annotation terms are assigned according to characteristics and functions specific for the respective gene. Term enrichment relative to the expected background distribution was scored using Fisher's exact test. Miltenyi´s TreeRanker system has two basic features that distinguish this software from other recently published approaches (77-79). In detail, annotations derived from fundamentally different sources (Gene ontology, gene families, sequence motifs, chromosomal proximity, literature keywords, etc) can be scored simultaneously for each given group of genes resulting in a joint statistical significance value. Furthermore, the scoring approach can be applied to entire hierarchical gene trees scoring individual sub-branch and reporting only non-redundant instances of significant annotation enrichment in specific clusters. In this mode a Bonferroni-correction was applied to the significance values accounting for the multiple-testing situations. Genes up- or down-regulated in both tumor-subtypes were subjected to further analysis with Interaction Explorer Software Pathway Assist (Version 2.5; Stratagene). The ResNet database (as of August 30, 2005) was searched for common cellular processes and protein complexes.

4.3.4 Functional Analysis of CD70

In order to test whether the up-regulation of *CD70* in RCC is functional for the tumor by provoking apoptotic cell death, lymphocyte co-culture experiments using the permanent RCC cell lines A498, CAKI1, and CAKI2 were performed. These adherent growing cells were co-cultured with the floating permanent T-cell cell line MOLT 4 and primary lymphocytes. For further details on culture conditions see chapter 4.2.2.

4.3.4.1 Expression of CD70, CD27, and SIVA in Permanent Cell Lines

CD70, CD27, and SIVA gene and protein expression in the permanent cell lines and in the primary lymphocytes was assessed via immunohistochemistry (IHC) and quantitative PCR (qPCR). For further details on the protocol see chapter 4.3.2.2. For qPCR, a QuantiTect® Primer Assay was purchased for the genes *CD27* and *SIVA* as well as for the reference gene *ILRAP1*. The design of the primer pair for *CD70* is described in chapter 4.3.2.2.

4.3.4.2 Analysis of Lymphocyte Apoptosis

MOLT4 cells were resuspended at a concentration of 1 x 10^6 cells/ml in sterile PBS 1640 (Gibco) before being added to flasks containing a RCC cell monolayer at a 1.5:1 tumor cell/lymphocyte ratio. Cells were co-cultivated in fetal calf serum (fcs)-free medium for 3 h. Floating lymphocytes were removed from the RCC cell monolayers and assessed for apoptosis using APO-One™ Homogeneous Caspase-3/7 Assay (Promega Madison, WI, USA) according to the manufacturer's directions. Blocking experiments were done by adding mouse monoclonal anti-human CD70 or mouse monoclonal anti-human-CD27 antibodies (both Ancell) when lymphocytes were incubated with the RCC monolayer. Both were used at a dilution of 5 µg/mL. The isotype control for the CD70 antibody was purified mouse immunoglobulin G_1 (Ancell). RmsCD70 was added to 1x10^6 cells/ml MOLT4 cells and native lymphocytes at a concentration of 50 ng/ml. Cells were cultivated in fcs-free medium for 3 hours before performing the apoptosis assay APO-One™ (Promega).

5 RESULTS

The results obtained from the protein and gene expression profiling of clear cell and papillary renal cell carcinoma are displayed in chapter 5.1 and 5.2. The results from the functional profiling of the gene expression data for both tumor-subtypes are shown in chapter 5.3. The results from the functional analysis of CD70 can be found in chapter 5.4. A combined summary of all results is given in chapter 5.5.

5.1 TRANSLATIONAL PROFILING

Translational profiling was carried out to find specific protein patterns for each tumor-subtype. The profiling was done for clear cell and papillary renal cell carcinoma and corresponding normal renal tissue. The resulting peak patterns were searched for tumor-specific candidates for marker proteins with two different bioinformatic analysis methods.

PATTERNS OF PROTEIN EXPRESSION ARE SPECIFIC FOR CLEAR CELL AND PAPILLARY RENAL CELL CARCINOMA. The SELDI spectra were compared in order to see if specific protein patterns for each tumor-subtype could be identified. A visual comparison reveals clear differences in the peak patterns found for papillary renal cell carcinoma (pRCC), clear cell renal cell carcinoma (ccRCC), and normal renal tissue (Figure 6). These differences are expressed as different intensities for a determined peak or even as the complete absence of a peak in one spectrum. The bioinformatic analyses of the spectra detected masses for which the expression levels were significantly different between normal and tumor tissue or between the two tumor-subtypes. These masses can be classified into four biologically relevant groups. These groups correspond to masses that are significantly differentially expressed:

1. in tumor tissue (both ccRCC and pRCC) versus normal renal tissue (normal)
2. between ccRCC and corresponding normal
3. between pRCC and corresponding normal
4. between ccRCC and pRCC

In the following paragraphs these groups are explained in more detail in order of appearance.

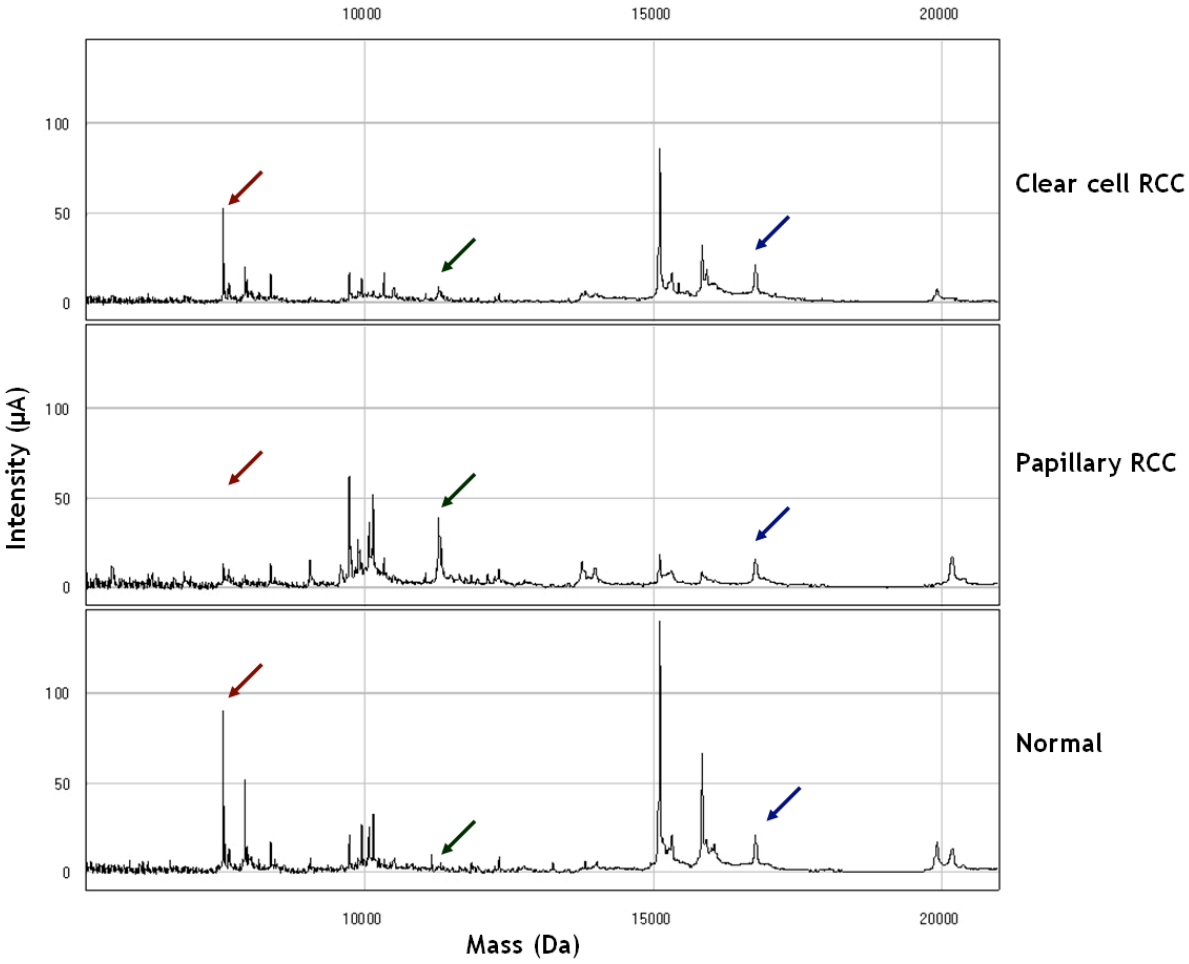


Figure 6 Representative examples of SELDI spectra for clear cell renal cell carcinoma, papillary renal cell carcinoma, and normal tissue. Visual comparison alone reveals differences in protein expression patterns (RCC= Renal cell carcinoma, Normal= Normal renal tissue; red and green arrows: peaks with a clear difference between normal and one tumor subtype, blue arrow: peaks with no difference between the analyzed tissues).

Group 1: Masses That Distinguish Between Normal Renal Tissue and Both Tumor-subtypes. A comparison of the protein spectra found 12 masses that have significantly different intensities in both clear cell renal cell carcinoma (ccRCC) and papillary renal cell carcinoma (pRCC) versus normal renal tissue (normal, Table 6). These 12 peaks differentiate between tumor tissue generally and normal. The peaks are all regulated in the same direction for both tumor-subtypes versus normal. Three masses (10347 Da, 10906 Da, and 11085 Da) were detected as being up-regulated in the tumor tissue and nine (3339 Da, 7561 Da 7599 Da, 11863 Da, 15125 Da, 15335 Da, 25595 Da, 30170 Da, and 31026 Da) were found to be down-regulated.

Table 6 Masses found with a statistically significant difference in intensity in clear cell renal cell carcinoma (ccRCC) and papillary renal cell carcinoma (pRCC) compared to normal renal tissue (Normal). Regulation given reflects direction of expression from normal. P-value was calculated with the software BiomarkerWizard™.

Mass (Da)	ccRCC versus Normal (p-value)	pRCC versus Normal (p-value)	Regulation
3339.9	0.00011	0.000002	Down
7561.43	0.00944	0.000363	Down
7599.91	0.00944	0.03	Down
10347.06	0.0024	0.00609	Up
10906.25	0.00097	0.00110	Up
11085.41	0.0311	0.0015	Up
11863.95	0.0386	0.0442	Down
15125.18	0.013	0.00064	Down
15335.86	0.02	0.0008	Down
25595.79	0.00004	0.000001	Down
30176.43	0.00009	0.00022	Down
31026.77	0.03	0.044	Down

Group 2: Masses That Distinguish Between Clear Cell Renal Cell Carcinoma and Corresponding Normal Renal Tissue. In general, the protein pattern found for clear cell renal cell carcinoma (ccRCC) shows a clear difference to the protein pattern for normal renal tissue (normal). Twenty-two masses with statistically significant differences in intensities were found which distinguish between ccRCC and normal. Six of these proteins or peptides are up-regulated in the tumor tissue compared to normal tissue and 16 of these proteins or peptides are down-regulated in the tumor tissue (Figure 10). Two of the 16 are particularly interesting because they have a very significant p-value: 25595 Da (p-value: 0.00004) and 30176 Da (p-value: 0.00009). A boxplot shows the difference in intensity of expression for these two peaks of interest between normal and tumor tissue (Figure 7). Interestingly, both masses also appear as being differentially expressed in papillary RCC (Table 6). The software XL-miner also identified them as being able to distinguish between ccRCC

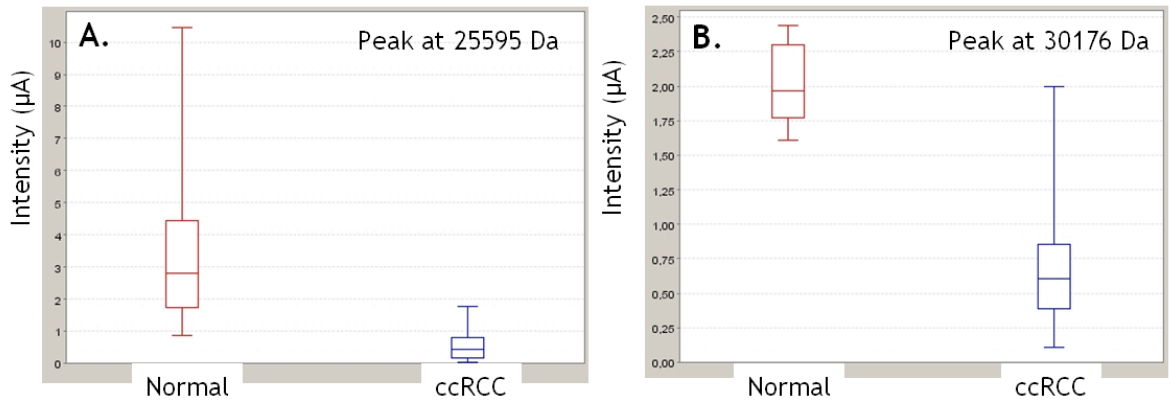


Figure 7 Boxplots of protein peaks of interest that can discriminate between clear cell renal cell carcinoma (ccRCC) and normal renal tissue (Normal) (p-values: for 25595 Da= 0.00004, for 30176 Da= 0.00009).

and normal renal tissue. The protein set found has a sensitivity of 95% and a specificity of 100%. Both proteins, or peptides, are specifically and consistently down-regulated in ccRCC tissue compared to normal renal tissue.

Group 3: Masses That Distinguish Between Papillary Renal Cell Carcinoma and Corresponding Normal Renal Tissue. The protein expression pattern found for papillary renal cell carcinoma (pRCC) shows a clear difference to the protein pattern for normal renal tissue. As expected, a notable difference can be seen compared to clear cell renal cell carcinoma (ccRCC). Forty-six masses with statistically significant differences in intensities were found which distinguish between pRCC and corresponding normal tissue. Interestingly, the number of statistically significant peaks detected in pRCC is twice as in ccRCC (Figure 10). Overall, 33 of these proteins or peptides are down-regulated in the tumor tissue compared to normal tissue and 13 proteins or peptides are up-regulated in the tumor tissue (Figure 10). In both tumor-subtypes an elevated number of down-regulated proteins or peptides were detected compared to normal renal tissue (Figure 10). Compared to the regulations found in ccRCC, the high number of down-regulated protein is notable.

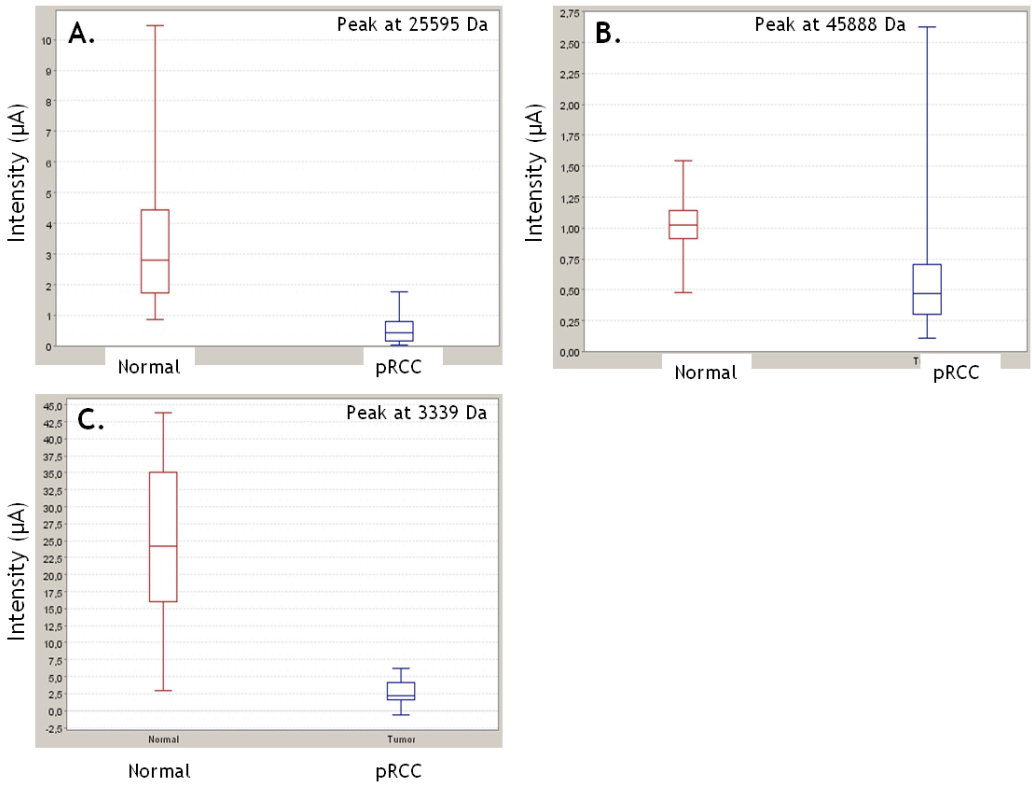
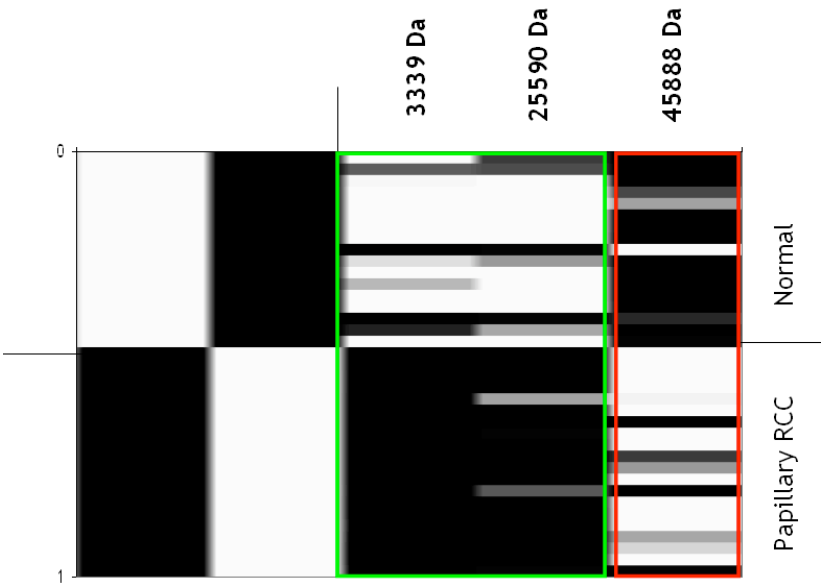


Figure 8 Boxplots of protein peaks of interest that can discriminate between papillary renal cell carcinoma (pRCC) and normal renal tissue (Normal, p-values: for 25585 Da= 0.000001, for 45888 Da= 0.0001, for 3339 Da= 0.000002).

A boxplot of the protein peaks of interest shows a clear difference in intensity of expression between normal and tumor tissue (Figure 8). Three peaks were identified with a very low p-value: 25595 Da (p-value: 0.000001), 45888 Da (p-value: 0.0001), and 3339 Da (p-value: 0.000002; Figure 9). This protein set has a sensitivity of 95% and a specificity of 88% (Figure 9). The peak at 3339 Da exhibits the most striking difference in intensity between pRCC tissue and normal renal tissue. Interestingly, the peak at 25595 Da was also found to be significantly different between ccRCC and normal renal tissue. The peak at 45888 Da seems to be highly specific for pRCC since it has not been detected as significantly regulated in ccRCC.



Condition (IF)	Conclusion (THEN)
Expression at peak 3339 Da high (>24.1)	Normal
Expression at peak 25590 Da high (>2.78)	Normal
Expression at peak 45888 Da low (<-0.46)	pRCC

Figure 9 Set of proteins and rules that distinguish between papillary renal cell carcinoma (pRCC) and normal renal tissue. Rule list (a = 95) with relevant rules for the prediction of pRCC (red frame) and normal renal tissue (green frame). Samples are clustered horizontally, peaks vertically. All expression values are log-2 transformed. The specificity of the combined rule base is 88%, the sensitivity is 95% (black: up-regulated, white: down-regulated, grey: no obvious tendency).

Group 4: Masses That Distinguish Between Clear Cell Renal Cell Carcinoma and Papillary Renal Cell Carcinoma. Fourteen proteins or peptides were found as being differentially expressed between clear cell renal cell carcinoma (ccRCC) and papillary renal cell carcinoma (pRCC). Five of these proteins or peptides were up-regulated in ccRCC compared to pRCC and nine proteins or peptides were down-regulated in ccRCC (Figure 10). As expected, the number of peaks found to be significantly different between the two tumor-subtypes is lower in comparison to

the peaks found between the tumor-subtypes and normal renal tissue (Figure 10). Furthermore, pRCC seems to be more different from normal renal tissue than ccRCC with regards to the number of statistically significant peaks. In total, more proteins or peptides were found to be down-regulated than up-regulated.

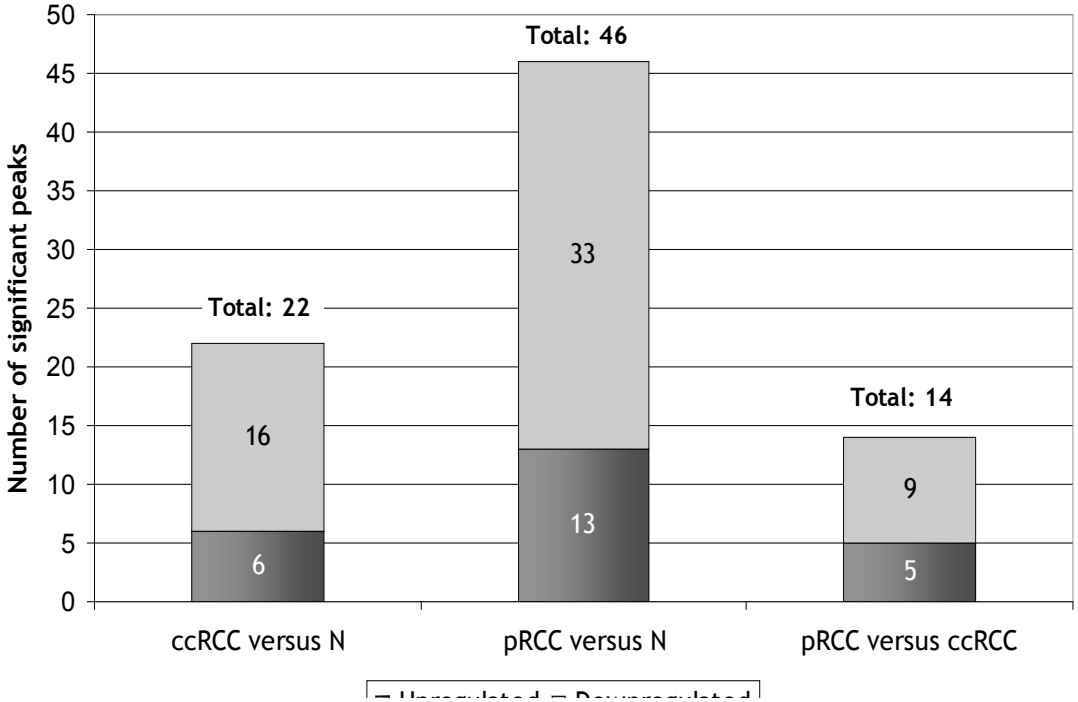


Figure 10 Number of peaks with a significant difference in intensity detected between the analyzed tumor and normal tissues (pRCC= papillary renal cell carcinoma, ccRCC= clear cell renal cell carcinoma, N= normal renal tissue).

Two peaks could be detected with a very low p-value: one peak at 9233 Da (p-value: 0.002) and one peak at 5829 Da (p-value: 0.00007). A boxplot of these two protein peaks shows the difference in intensity of expression between ccRCC and pRCC (Figure 11).

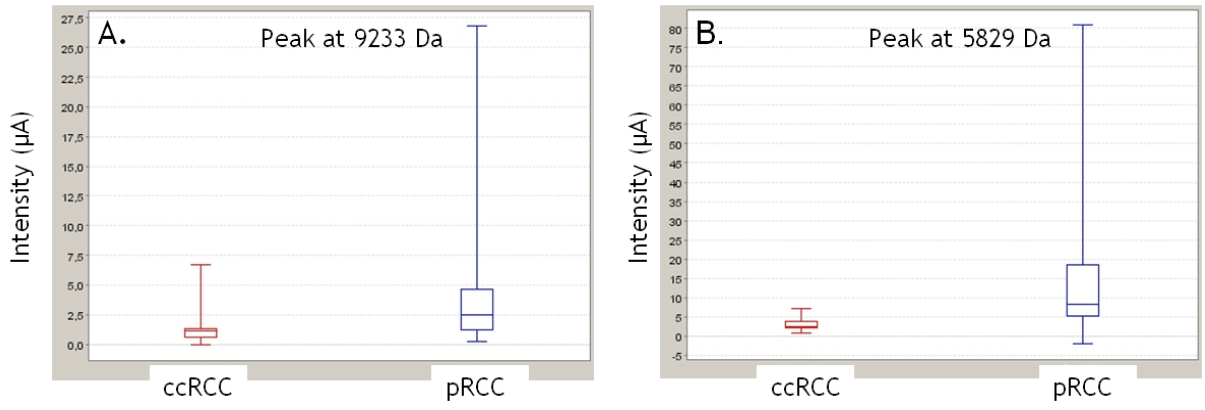
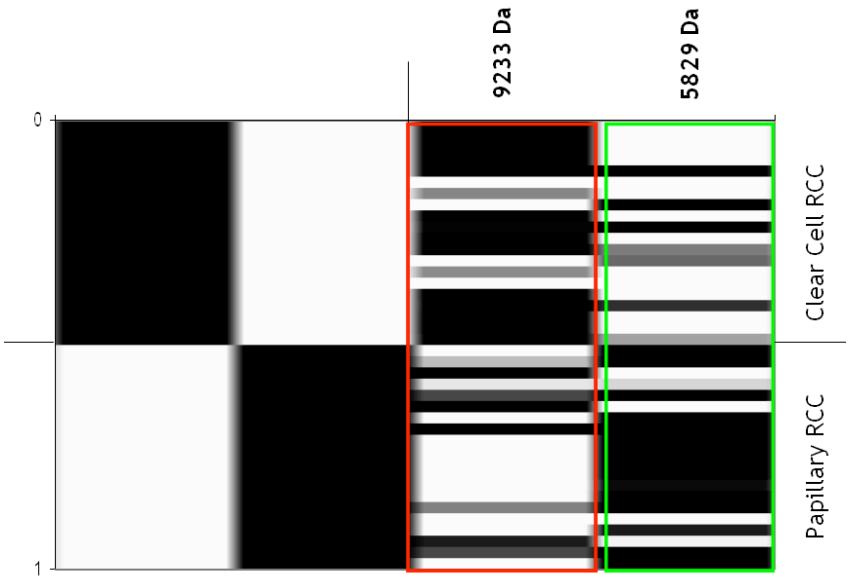


Figure 11 Boxplots of protein peaks of interest that can discriminate between clear cell renal cell carcinoma (ccRCC) and papillary renal cell carcinoma (pRCC; p-values: for 9233 Da= 0.002 for 5829 Da= 0.00007).

This protein set has a sensitivity of 75% and a specificity of 100% (Figure 12).



Condition (IF)	Conclusion (THEN)
Expression at peak 9233 Da low (<-1.28)	ccRCC
Expression at peak 5829 Da high (>1.69)	pRCC

Figure 12 Set of proteins and rules that distinguish between clear cell renal cell carcinoma (ccRCC) and papillary renal cell carcinoma (ccRCC). Rule list (a = 85) with relevant rules for the prediction of pRCC (red frame) and ccRCC (green frame). Samples are clustered horizontally, peaks vertically. All expression values are log-2 transformed. The specificity of the combined rule base is 100%, the sensitivity is 79% (black: up-regulated, white: down-regulated, grey: no obvious tendency).

5.2 Transcriptional Profiling

The transcriptional profiling was carried out to find specific gene expression patterns for each tumor-subtype. The profiling was done for clear cell and papillary renal cell carcinoma and corresponding normal renal tissue. A description of the genes found is given in the next chapter.

Microarray Analysis – 325 Genes (50 %) Found To Be Differentially Expressed in Clear Cell Renal Cell Carcinoma. A total of 325 genes (50.1% of genes present) were found to be more than two-fold differentially expressed in at least one tumor sample compared to corresponding normal renal tissue. Cluster analysis was performed to search for commonly up- or down-regulated gene clusters and found several gene clusters with a very homogeneous expression pattern (Figure 13).

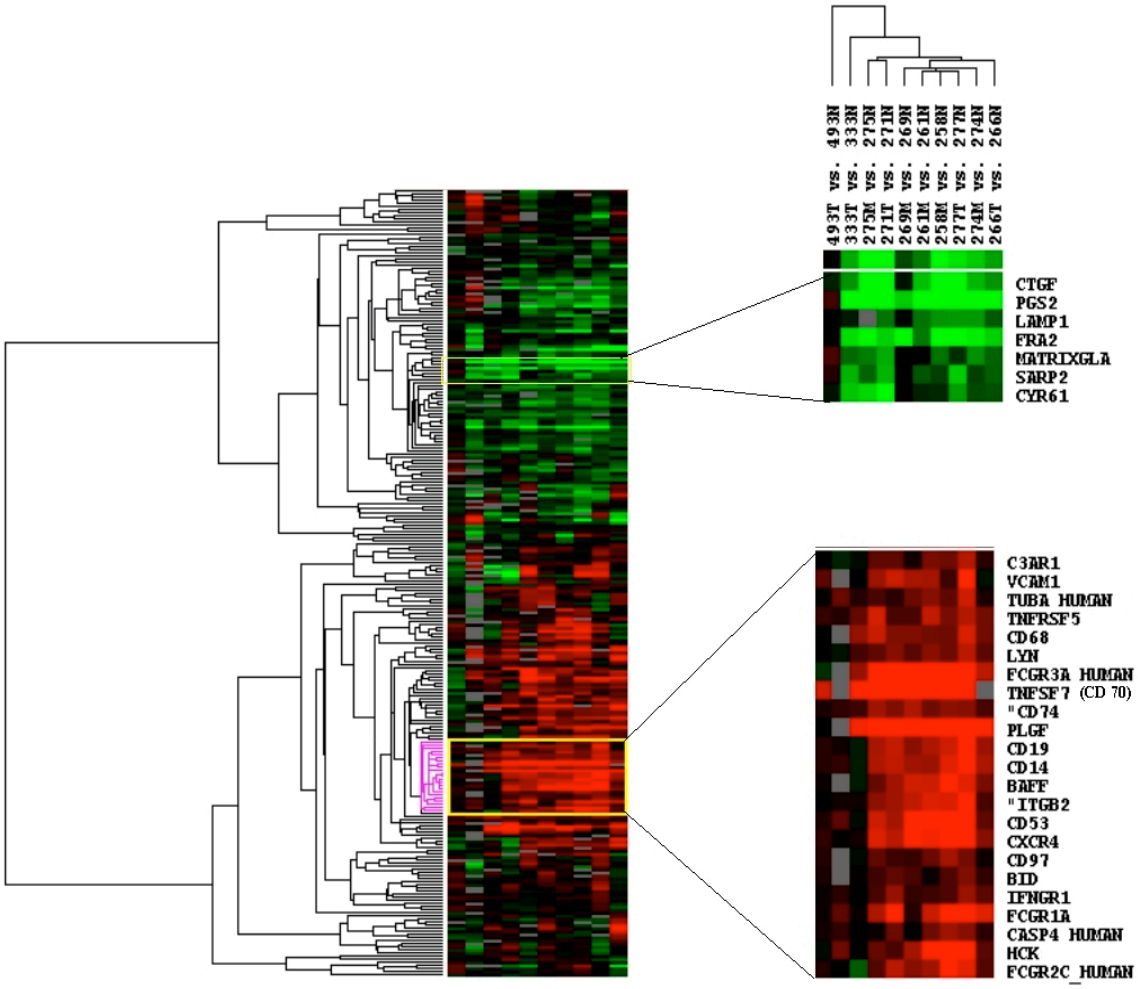


Figure 13 Cluster analyses of genes found in clear cell renal cell carcinoma, detectable in all microarray experiments with an enlargement of two areas of interest with down- and up-regulated genes (Figure legend: T and M = tumor tissue, N = normal tissue, red color: up-regulation, green color: down-regulation).

Among the genes detected, some were previously described as differentially regulated, but some are possibly new marker genes for ccRCC (the entire gene list with all results is shown in 'Appendix II'). A list comparing the genes found to be regulated in this study with genes identified by other groups is shown in Table 7.

Table 7 Genes found as being differentially expressed in clear cell renal cell carcinoma in this study previously identified and described by other groups.

Gene name	Unigene Number	Patients showing ≥ two fold expression (Percent)	Previously described
CALB1	Hs. 1285	50%	Martignoni and colleagues, 2001
CCND1	Hs. 371468	70%	Stassar and colleagues, 2001
Collagen type II	Hs. 408182	50%	Droz and colleagues, 1994
Collagen type IV	Hs. 407912	50%	Droz and colleagues, 1994
CXCR4	Hs. 421986	70%	Schrader and colleagues 2002
HEVIN	Hs. 75445	80%	Gerritsen and colleagues, 2002
Integrin type alpha I	Hs. 519305	50%	Droz and colleagues, 1994
Integrin type alpha 5	Hs. 149609	50%	Droz and colleagues, 1994
Integrin type beta 2	Hs. 375957	60%	Droz and colleagues, 1994
LINK	Hs. 2799	30%	Boer, and colleagues, 2001
LOX	Hs. 102267	30%	Lenburg, and colleagues, 2003
PAI1	Hs. 356427	60%	Swiercz and colleagues, 1998)
VCAM1	Hs. 109225	50%	Droz and colleagues, 1994
VEGF	Hs. 135039	80%	Gerritsen and colleagues, 2002; Takahashi and colleagues, 1999
VWF	Hs. 440848	60%	Braybrooke and colleagues, 2000

Regulations were confirmed for the genes *collagen type II* and *IV* as well as *integrin, type alpha, 1* and *5*, and *beta, type 2*. Of special interest is the gene *CXCR4* which was already described as a potential biomarker for RCC (16). Here, *CXCR4* was found to be up-regulated in seven of ten tumor samples. Moreover, several so far unknown genes for ccRCC were identified as being differentially expressed (Table 8).

Table 8 Previously unidentified genes found to be differentially expressed in clear cell renal cell carcinoma.

Gene	Unigene Number	Patients showing ≥ two fold expression (Percent)	Induction (x-fold)
Pgs2	Hs. 156316	90%	0.074
Fosl2	Hs. 220971	90%	0.259
Tpa	Hs. 491582	90%	0.294
CD70	Hs. 99899	80%	39

The four most prominent genes identified are *PGS2, FOSL2, TPA*, and *CD70*. A down-regulation in the majority of the examined samples has been found for *PGS2*,

FOSL2, and *TPA*. However, the drastic induction of the gene *CD70* (average of 39-fold) in tumor tissue is of special interest.

MICROARRAY ANALYSIS – 602 GENES (56%) FOUND TO BE DIFFERENTIALLY EXPRESSED IN PAPILLARY RENAL CELL CARCINOMA. A total of 602 genes (55.7% of genes present) were found to be more than two-fold differentially expressed in at least one tumor sample compared to corresponding normal renal tissue. Cluster analysis was performed to search for commonly up- or down-regulated gene clusters in pRCC and an overview of the results is shown in Figure 14.

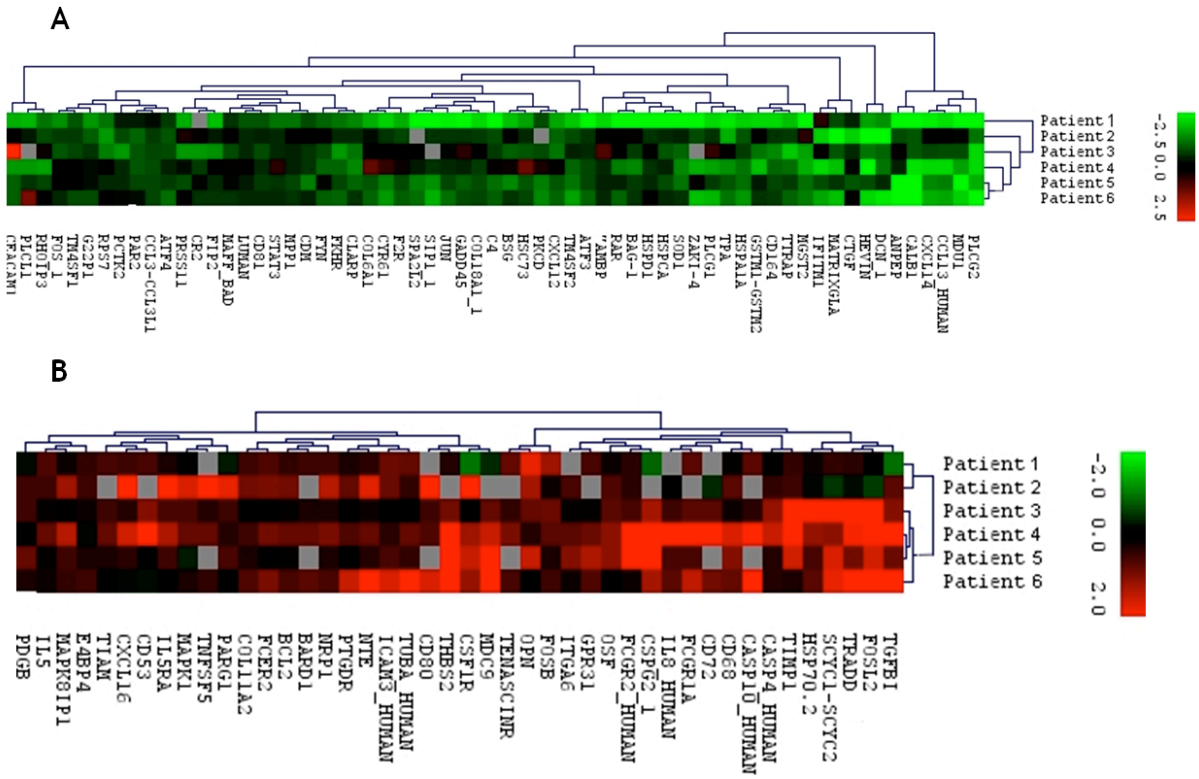


Figure 14 Overview of up- and down-regulated genes in papillary renal cell carcinoma. A. Down-regulated B. Up-regulated (Red color: up-regulation, green color: down-regulation).

As with ccRCC, several of the genes found to be differentially regulated for pRCC had been previously described but several new possible marker genes were also identified (the entire gene list with all results can be found in 'Appendix II'). Two genes already known to be differentially regulated, *TIMP1* and *THBS2*, were confirmed as being up-regulated in pRCC (80;81). Furthermore, several previously identified genes (for example genes with relevance to the extracellular matrix) were confirmed to be differentially expressed such as *CEACAM 1, C-Kit, IGFBP6, CXCR4, TIMP 1, MMP-9, CD34, CD44,* and *Gro-1*. A list comparing the genes found to be regulated in this study with genes identified by other groups is shown in Table 9. Additionally, a slight but nevertheless consistent over-expression of the genes

TNFR1, *TNFRSF10b*, and *CD70* was detected. These three genes were also found to be up-regulated in ccRCC in this study.

Table 9 Genes found to be differentially expressed in papillary renal cell carcinoma in this study previously described by other groups.

Gene name	Unigene Number	Patients showing ≥ two fold expression (Percent)	Previously described
CEACAM1	Hs. 512682	50%	Kammerer and colleagues, 2004
CD36	Hs. 120949	87.5%	Gerritsen and colleagues, 2002
C-Kit	Hs. 479754	50%	Petit and colleagues , 2004
CXCR4	Hs. 421986	50%	Gerritsen and colleagues 2002; Bhaskar and colleagues, 2001
IGFBP6	Hs. 274313	50%	Takahasi and colleagues, 2003
MMP-9	Hs. 297413	25%	Gerritsen and colleagues, 2002
Nidogen	Hs. 356624	50%	Gerritsen and colleagues, 2002
PECAM	Hs. 514412	50%	Gerritsen and colleagues, 2002
SPARC	Hs. 111779	50%	Gerritsen and colleagues, 2002
TIMP1	Hs. 522632	75%	Gerritsen and colleagues, 2002
TIMP2	Hs. 104839	87.5%	Bhaskar and colleagues, 2001
Thrombospondin 2	Hs. 371147	50%	Gerritsen and colleagues, 2002
Thrombospondin 4	Hs. 211426	62.5%	Gerritsen and colleagues, 2002
VEGF	Hs. 135039	25%	Gerritsen and colleagues, 2002

A total of seven genes that have not previously been described for pRCC were found to be differentially expressed (Table 10). The gene with the most prominent down-regulation in pRCC is *CALB1* (0.35-fold), but also *CCL13*, *CXCL14*, and *PLCG2* are consistently and strongly down-regulated in most samples (Table 10). All differentially expressed genes can be found in 'Appendix II'.

Table 10 Previously undescribed genes identified to be differentially expressed in papillary renal cell carcinoma.

Gene Name	Unigene Number	Patients showing ≥ two fold expression	Induction (x-fold)
CCL13	Hs. 54460	83%	0.57
CXCL14	Hs. 100431	83%	0.53
CALB1	Hs. 1285	83%	0.35
MDU1	Hs. 81874	83%	0.6
PLCG2	Hs. 270411	50%	0.51
CD68	Hs. 445570	83%	1.7
CD37	Hs. 349656	83%	2.25

The inductions of *CD68, CD37, CALB1, and MDU1* expression were among the strongest inductions found among all 1070 analyzed genes for pRCC and were observed in over 80% of the performed experiments.

5.2.1 CONFIRMATION OF DIFFERENTIALLY EXPRESSED GENES

CD70 OVER-EXPRESSION IN CLEAR CELL RENAL CELL CARCINOMA WAS CONFIRMED WITH QUANTITATIVE PCR. Quantitative PCR (qPCR) was performed with all samples that have been previously examined on cDNA-microarrays. Two genes were selected to be confirmed by qPCR: *FOSL2* and *CD70* (Table 11). They were chosen due to their high potential to discriminate between normal and tumor tissue. One study had previously detected *CD70* as up-regulated in renal cell carcinoma (RCC) by microarray experiments but no confirmation with array-independent methods was carried out (82). The down-regulation of *FOSL2* in RCC has not been reported so far.

Table 11 Qualitative correlation of microarray and quantitative (qPCR) data for clear cell renal cell carcinoma of *CD70* and *FOSL2*. The percentage of samples in which the respective gene is >two-fold regulated is shown for both expression profiling platforms (the qPCR experiments were performed in triplicates and the standard deviation in all experiments performed lies between 0.02 and 1.9 %).

Regulated gene	Unigene Number	Patients showing ≥ two fold expression by microarray (Percent)	Patients showing ≥ two fold expression by qPCR (Percent)
CD70	Hs. 99899	80%	80%
FOSL2	Hs. 220971	90%	50%

In order to compare the quantified mRNA molecules of the candidate genes in the relative expression ratio model, *MCP* was chosen as the reference gene for ccRCC because it showed no significant regulation on any hybridized microarray. The qPCR efficiency was set to 2 (E = 2.0) for all factors. For the gene *CD70,* relative expression data derived from microarrays and LightCycler experiments is shown as an example in Figure 15.

The induction of *CD70* gene expression was among the strongest inductions found of all genes that have been analyzed. In two microarray experiments in which *CD70* was not detectable, a modest repression of the gene was found via qPCR. The repression of the gene *FOSL2* could only be seen in 50% of the examined samples.

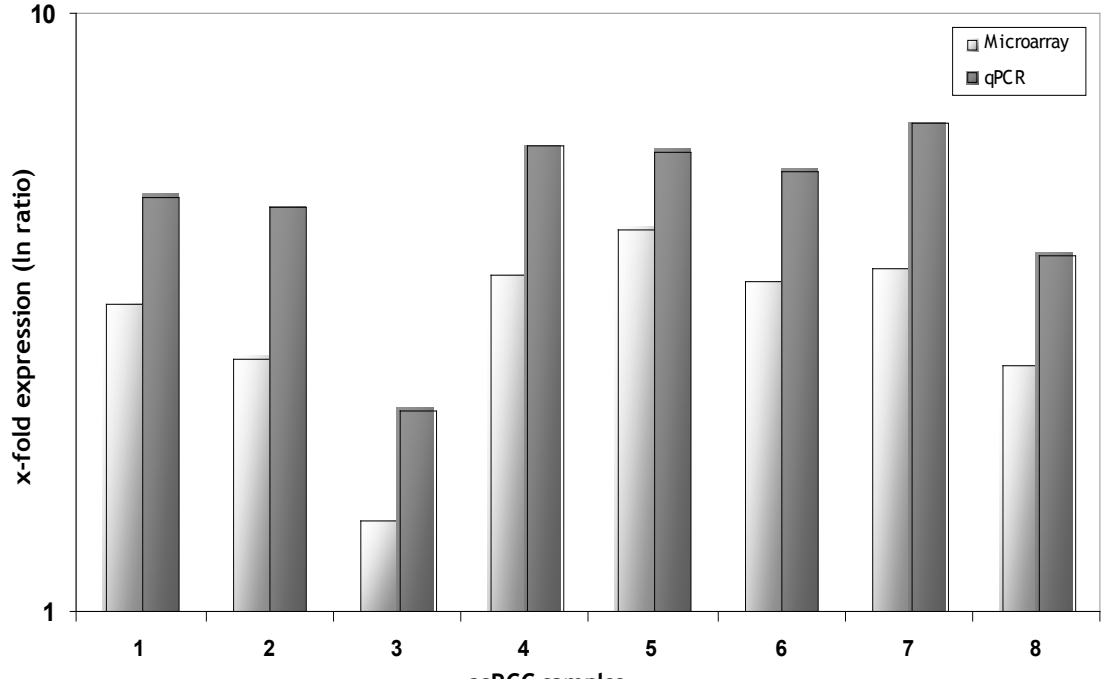


Figure 15 Comparison of *CD70* expression of clear cell renal cell carcinoma (ccRCC) versus normal tissue analyzed either by microarray or quantitative PCR (qPCR) technology (the qPCR experiments were performed in triplicates and the deviation within the standard error lies between 0.02 and 1.9%).

ALL SELECTED GENES, CD37, CALB1, MDU1, AND CD68 COULD BE CONFIRMED WITH QUANTITATIVE PCR AS BEING DIFFERENTIALLY EXPRESSED IN PAPILLARY RENAL CELL CARCINOMA. Quantitative PCR (qPCR) was performed with the same samples previously examined with cDNA-microarrays. Additionally, a total of six samples that had not been analyzed with cDNA-microarrays were subjected to qPCR. A subset of genes (*CD37, CALB1, MDU1,* and *CD68*) found to be differentially expressed was confirmed via qPCR in over 70% of the examined samples (Table 12). All four genes showed a high potential to discriminate between normal and tumor tissue.

Table 12 Qualitative correlation of cDNA-microarray and quantitative PCR (qPCR) data for papillary renal cell carcinoma of four selected genes that seem to be discriminative between normal versus tumor tissue. The number of patients in which the respective gene is >2-fold regulated is shown for both expression profiling platforms (the qPCR experiments were performed in triplicates).

Regulated gene	Unigene Number	Results from cDNA-microarray (Percent)	Results from qPCR (Percent)
CD37	Hs. 349656	87.5%	75%
CD68	Hs. 445570	87.5%	83%
MDU1	Hs. 81874	100%	83%
CALB1	Hs. 1285	87.5%	83%

In order to compare the quantified mRNA molecules of the candidate genes in the relative expression ratio model, *IL1RAP* was chosen as the reference gene because

it showed no significant regulation on all hybridized microarrays. The qPCR efficiency was set to 2 (E = 2.0) for all factors. The standard deviation in all experiments performed lies between 0 and 3.38%. The regulations found by cDNA-microarrays were confirmed for all four genes by qPCR (Table 13).

Table 13 Comparison of candidate gene expression of tumor versus normal tissue analyzed either by microarray or quantitative PCR (qPCR) technology (the qPCR experiments were performed in triplicates, green color: consistent results, yellow color: deviant results, n.m = not measured).

	***CD37* x-fold induction**		***CD68* x-fold induction**		***MDU1* x-fold induction**		***CALB1* x-fold induction**	
Sample	qPCR	Microarray	qPCR	Microarray	qPCR	Microarray	qPCR	Microarray
1	n.m	1.55	0.06	1.92	9 E-07	0.26	n.m	0.15
2	435	1.26	278	2.4	0.4	0.27	0.059	0.13
3	1.2	1.4	2.4	1.14	0.01	0.16	0.1	0.17
4	0.6	1.6	1.3	1.25	0.1	0.1	0.06	0.7
5	14	n.m	12.8	n.m	0.3	0.27	7 E-06	0.16
6	0.07	1.63	0.62	1.68	0.1	0.35	0.003	0.22
7	210	1.2	39	1.24	n.m	1.6	6.6	0.52
8	27.4	1.2	5.5	3.25	0.2	0.1	0.025	n.m
9	1.2	n.m	26.7	n.m	0.3	n.m	0.05	n.m
10	7.5	n.m	16.1	n.m	9.2	n.m	0.0024	n.m
11	121	n.m	12	n.m	0.2	n.m	0.0002	n.m
12	3	n.m	1.3	n.m	0.02	n.m	0.0004	n.m

CD70 COULD ADDITIONALLY BE CONFIRMED AS BEING DIFFERENTIALLY EXPRESSED WITH IMMUNOHISTOCHEMISTRY. To test if the induction on the mRNA level in the tumor samples is also reflected at the protein level, the localization of three molecules found in this study (*CD70*, *CD37*, and *FOSL2*) was examined by immunohistochemistry (IHC). The immunohistochemical staining for CD37 and FOSL2 were inconsistent and showed no conclusive discrimination between normal and tumor tissue. A positive staining for these proteins could only be observed in two out of ten cases. In contrast, IHC for CD70 clearly confirmed its differential expression (Table 14).

A total of 68 tumor samples were analyzed for CD70, including 41 ccRCC (which includes those that were also analyzed via microarray and qPCR), 19 pRCC (which includes those that were also analyzed via microarray and qPCR), five chromophobe RCC, and three oncocytomas (Table 14).

Table 14 Results after immunostaining with anti-CD70 antibody in different tumor types and in corresponding normal tissue (RCC= Renal cell carcinoma, No.= number, from Junker et.al (83).

RCC type	Tumor (no./Total No.)	Normal (no./Total No.)
Clear cell	41/41	0/41
Papillary	1/19	0/19
Chromophobe	1/5	0/5
Oncocytoma	0/3	0/3

In each tissue section, more than 80 % of the tumor cells were stained. Corresponding normal kidney tissues were investigated in parallel. No immunostaining was detected in any normal sample (Table 14 and part A of Figure 16). Negative controls showed the expected negative results for all antibodies used.

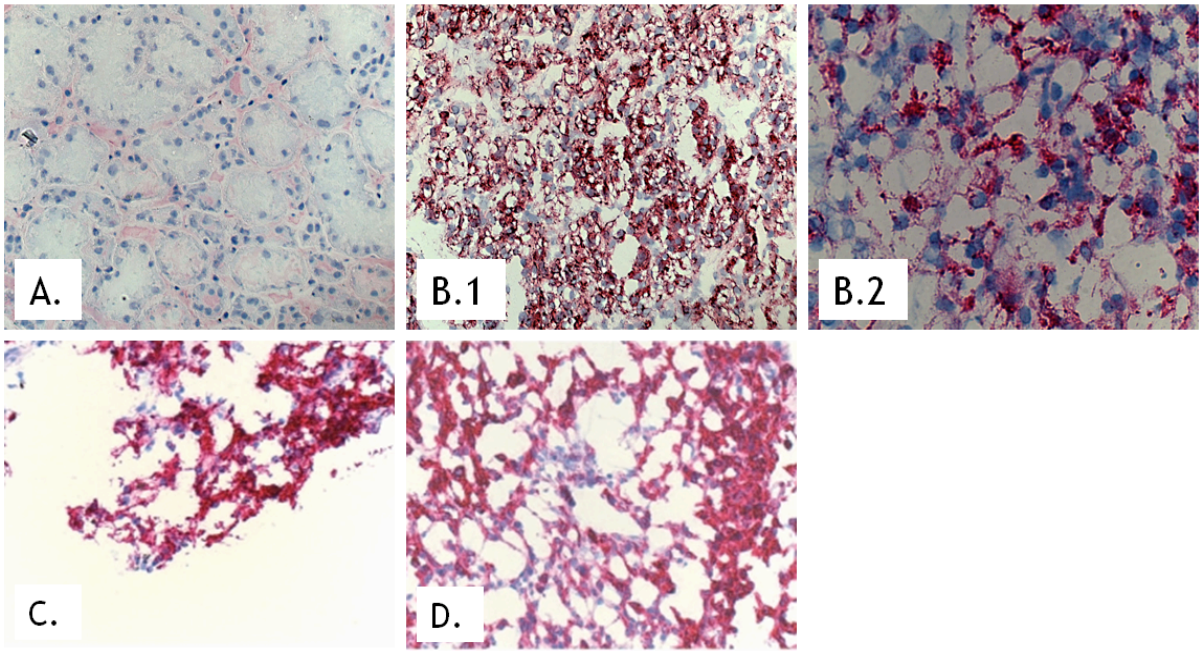


Figure 16 Immunostaining for *CD70* on frozen sections of A. normal tissue (x200) and corresponding clear cell renal cell carcinoma B.1. (x200) and B.2. (x350) C. papillary renal cell carcinoma and D. chromophobe renal cell carcinoma (x200). Red color indicates presence of the protein of interest.

All ccRCC samples showed high CD70 expression in least 80% of the cells (part B.1 and B.2 of Figure 16). Staining was accentuated in the tumor cell membrane, but was also weakly detected within the cells (Figure 16). No immunoreactivity could be detected in the surrounding stroma. Only in one pRCC sample high expression of CD70 was found (part *C* of Figure 16). However, histopathological classification was not reliable in this case. Focal immunostaining (less than 5%) occurred in five additional pRCC samples. One out of five chromophobe RCC expressed CD70 at a high level (part *D* of Figure 16). However, it was difficult to classify this tumor. No oncocytoma showed immunostaining for CD70.

5.3 FUNCTIONAL PROFILING

The functional profiling was carried out to find functional connections between the regulated genes for each tumor-subtype. The profiling was done for clear cell and papillary renal cell carcinoma (ccRCC and pRCC) and corresponding normal renal tissue. In order to compare the datasets generated by transcriptional profiling only those genes that were present on both topic-defined cDNA-microarrays were subjected to the functional profiling (chapter 4.3.2.1). For the comparative functional analysis, the gene expression dataset of pRCC was compared with the gene expression dataset of ccRCC. First, a global correlation analysis was performed to find out whether the gene expression profiles of patients belonging to the same tumor-subtype cluster together. Second, each dataset was searched for genes similarly regulated. Third, a functional annotation analysis was performed if a sufficient number of regulated genes were identified (Figure 17).

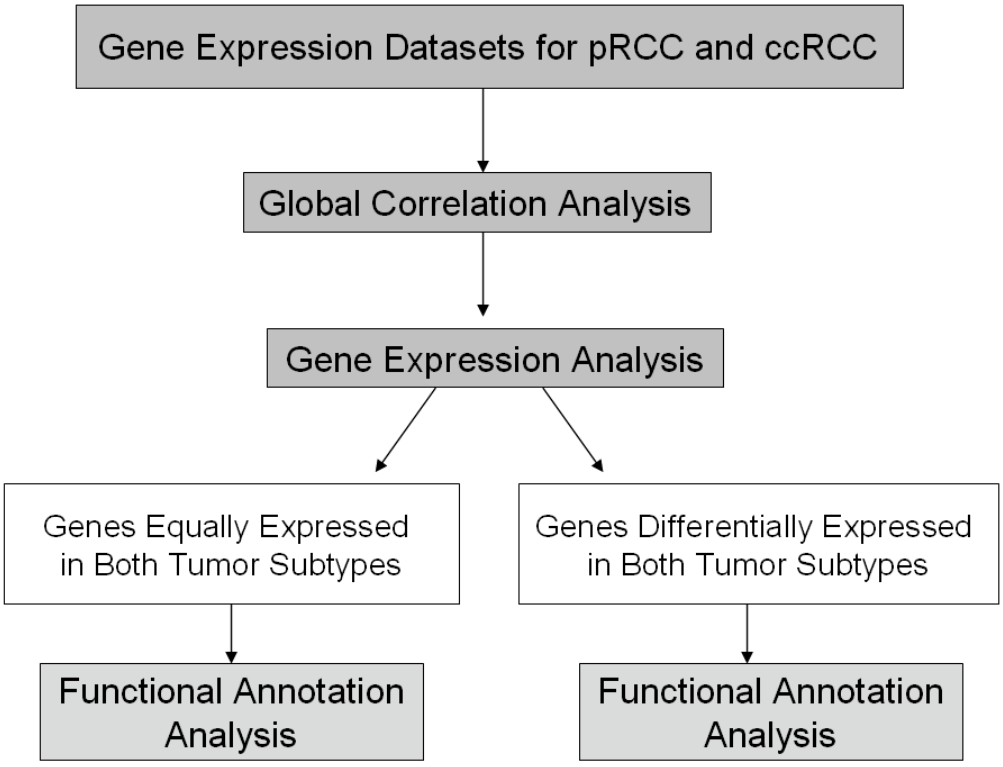


Figure 17 Overview of the analysis design for the functional profiling (pRCC = papillary renal cell carcinoma, ccRCC = clear cell renal cell carcinoma).

GLOBAL CORRELATION ANALYSIS OF GENE EXPRESSION DATASETS SHOWS THAT TUMOR-SUBTYPES CLUSTER SEPARATELY. The correlation between the expression profiles of the datasets for clear cell and papillary RCC gene expression was assessed (Figure 18). For this purpose, all genes that were found to be expressed in at least 55% of the samples were used. The expression profiles of both datasets satisfactorily cluster in clearly separable groups (Figure 18).

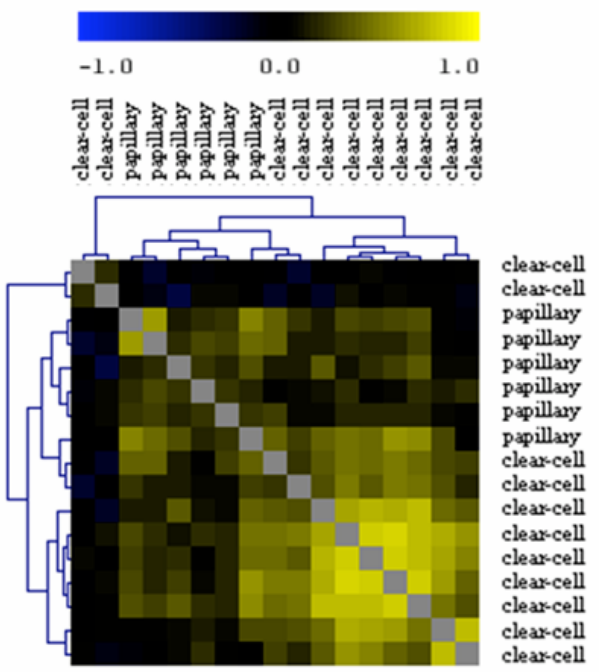


Figure 18 Global inter-experiment correlation analysis of genes present on both topic-defined PIQOR™ microarray compositions. Yellow color indicates good correlation between two expression profiles while black squares represent poor or even anti-correlation (blue).

Two samples of the ccRCC dataset show a very divergent expression profile, neither matching to the other ccRCC samples nor to the pRCC samples. Additionally, one experiment belonging to the pRCC dataset fits better to the ccRCC dataset. A closer inspection of patient data (e.g. histology, age, gender, and other pathologically relevant data) did not reveal possible reasons for these outliers.

Gene Regulations in Papillary and Clear Cell Renal Cell Carcinoma. The comparative functional analysis revealed genes that were regulated in both tumor-subtypes in the same direction (equally) as well as genes that were differentially regulated. These genes can be divided into two groups:

1. Discriminative genes for both tumor-subtypes.
2. Genes equally expressed in both tumor-subtypes.

Group 1: Discriminative Genes for Both Tumor-Subtypes. The differentially expressed genes in both tumor-subtypes comprise thirteen genes that are up-regulated in the ccRCC samples and down-regulated in the pRCC samples (Figure 19). This gene set distinguishes between the tumor-subtypes applying a false-discovery rate of zero to the combined dataset. Only one gene (*FOSL2*) was found to be consistently up-regulated in pRCC and consistently down-regulated in ccRCC. *CD70* as well as *PLGF* are strongly up-regulated (39-fold and 20.8-fold, respectively) in all ccRCC samples, but only weakly (1.2-fold and 1.1-fold, respectively) in the pRCC samples. *FOSL2* and *HEVIN* exhibit the most contrary expression between the tumor-subtypes.

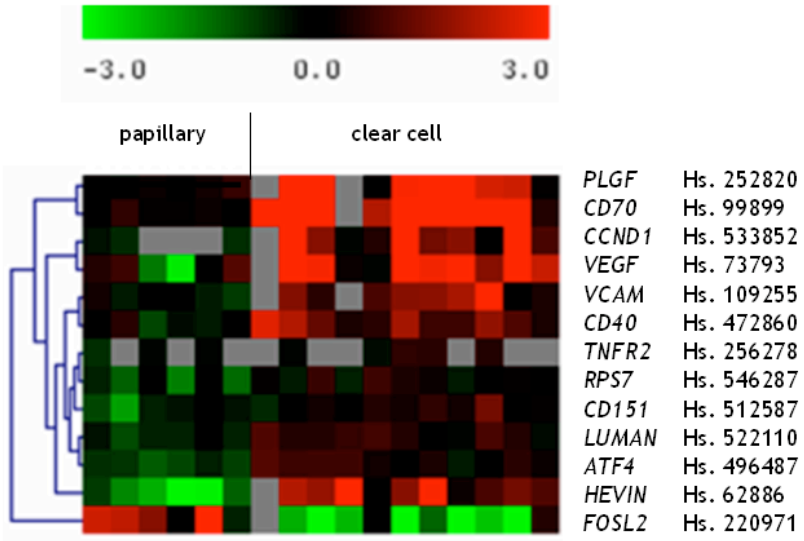


Figure 19 Overview of genes discriminating between the clear cell and papillary renal cell carcinoma datasets (Unsupervised one-dimensional clustering of log2 data using the 'Euclidean distance' metric, red color: up-regulated in tumor tissue, green color: down-regulated, black color: no regulation, grey color: not measured).

GROUP 2: GENES EQUALLY EXPRESSED IN BOTH TUMOR-SUBTYPES. Forty-five genes were identified to be regulated equally in both RCC subtypes (Table 15). They were grouped according to their characteristics and functional annotations. The down-regulated genes in both tumor-subtypes are mostly enzymes (ten genes) or genes involved in lipid and carbohydrate metabolism (Table 15). Among the up-regulated genes in both tumor-subtypes was a significantly relevant group of 12 genes representing surface markers. Both groups were subjected to a functional annotation analysis.

Table 15 Overview of genes up- or down-regulated in both examined renal cell carcinoma subtypes (m.a. = multiple annotation, no. = number).

Genes down-regulated in both tumor-subtypes			Genes up-regulated in both tumor-subtypes		
Gene Name	**Unigene No.**	**Annotation**	**Gene Name**	**Unigene No.**	**Annotation**
CCNH	Hs.514	DNA-metabolism	*TNFR1*	Hs.159	surface marker
BAMACAN	Hs.24485	DNA-metabolism	*BAFF*	Hs.270737	surface marker
HSPA1A/HSPA1B	Hs.432648	DNA-metabolism/HSP70	*TNFRSF10B*	Hs.521456	surface marker
ANPEP	Hs.1239	Enzyme	*PMP22*	Hs.76556	surface marker
SOD1	Hs.75428	Enzyme	*PDGFRB*	Hs.30778	surface marker
FYN	Hs.439387	Enzyme	*CD53*	Hs.82212	surface marker
PLAT	Hs.248197	Enzyme	*FCGR1A*	Hs.77424	surface marker
RAR	Hs.307905	Enzyme	*CD68*	Hs.445570	surface marker
PLCL	Hs.355888	enzyme/lipid	*CD70*	Hs.177136	surface marker
PRKCL2	Hs.349611	enzyme/lipid	*CD19*	Hs.96023	surface marker
PRSS11	Hs.46	enzyme/lipid	*FCGR2*	Hs.78864	surface marker
PIK3CB	Hs.239818	enzyme/lipid	*CD45*	Hs.306278	surface marker
PLCG2	Hs.75648	enzyme/lipid	*IL8*	Hs.194778	m.a
HSPA8	Hs.1570	HSP70	*IL16*	Hs.82127	m.a
HSPA9	Hs.3268	HSP70	*TUBA*	Hs.278242	m.a
CTGF	Hs.75511	lipid metabolism	*CASP4*	Hs.141125	m.a
CYR61	Hs.8867	lipid metabolism	*BID*	Hs.172894	m.a
COL18A1	Hs.413175	m.a	*PLGF*	Hs.2894	m.a

Continuation of Table 15

Genes down-regulated in both tumor-subtypes			Genes up-regulated in both tumor-subtypes		
Gene Name	**Unigene No.**	**Annotation**	**Gene Name**	**Unigene No.**	**Annotation**
COL6A1	Hs.26208	m.a	*CSK*	Hs.77793	m.a
LTBP4	Hs.85087	m.a	*CX3CR1*	Hs.80420	m.a
DCN	Hs.83974	m.a	*SPARC*	Hs.333175	m.a
ATF5	Hs.9754	m.a	*STAT1*	Hs.21486	m.a
BACH1	Hs.154276	m.a			

FUNCTIONAL ANNOTATION ANALYSIS REVEALS MECHANISMS ENABLED IN BOTH TUMOR-SUBTYPES. The aim was to search for common cellular processes enabled in RCC according to their annotations. The relations found for the up-regulated genes are shown in Figure 20 and for the down-regulated genes in Figure 21. A better visualization of the connections found was achieved by displaying the specific functions of the genes rather than general annotations.

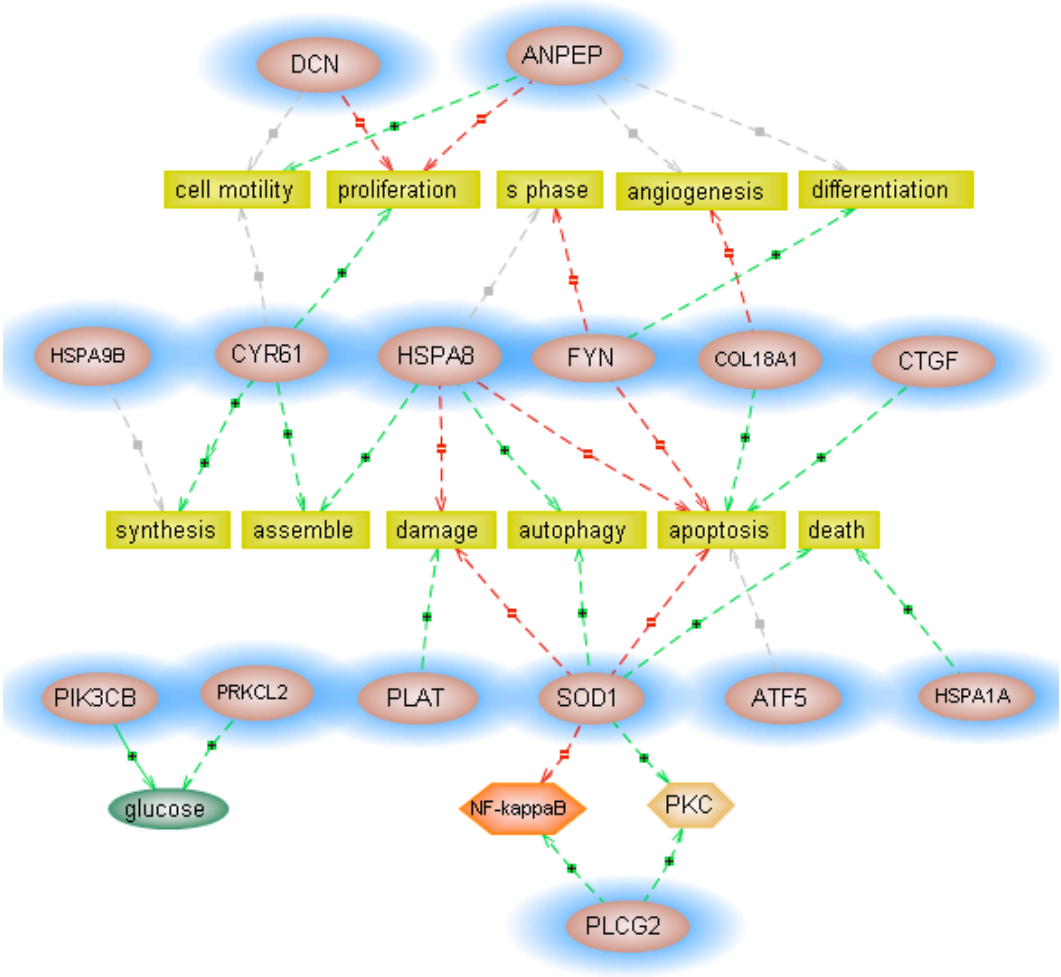


Figure 20 Network analysis of the genes that are down-regulated in both tumor-subtypes (blue halo) to identify common cellular processes (yellow boxes) and protein complexes (hexagons; green arrow: activation, red arrow: inhibition, grey arrow: unknown influence).

The genes that are down-regulated in both tumor-subtypes encode mostly for enzymes or are genes which encode for proteins that are related to the lipid and

carbohydrate metabolism (Table 15). A detailed visualization of all relations found is given in Figure 20. Several down-regulated genes (*CTGF, ATF5, SOD1, HSPA8, FYN, COL18A1, and HSPA1a*) were found that are related to apoptosis or cell death (Figure 20). There are also genes down-regulated in both tumor-subtypes that are related to cell motility and proliferation, like *ANPEP, DCN*, and *CYR61* (Figure 20). For the 22 genes that are up-regulated in both tumor-subtypes, more complex connections could be detected (Figure 21). Ten out of these 22 genes have multiple annotations even though most of them are related to cell motility (Figure 21). However, more than 50% of these 22 genes up-regulated in both tumor-subtypes belong to the annotation “surface markers”. A closer look at the function of those surface markers revealed their possible involvement in apoptotic processes and immune response.

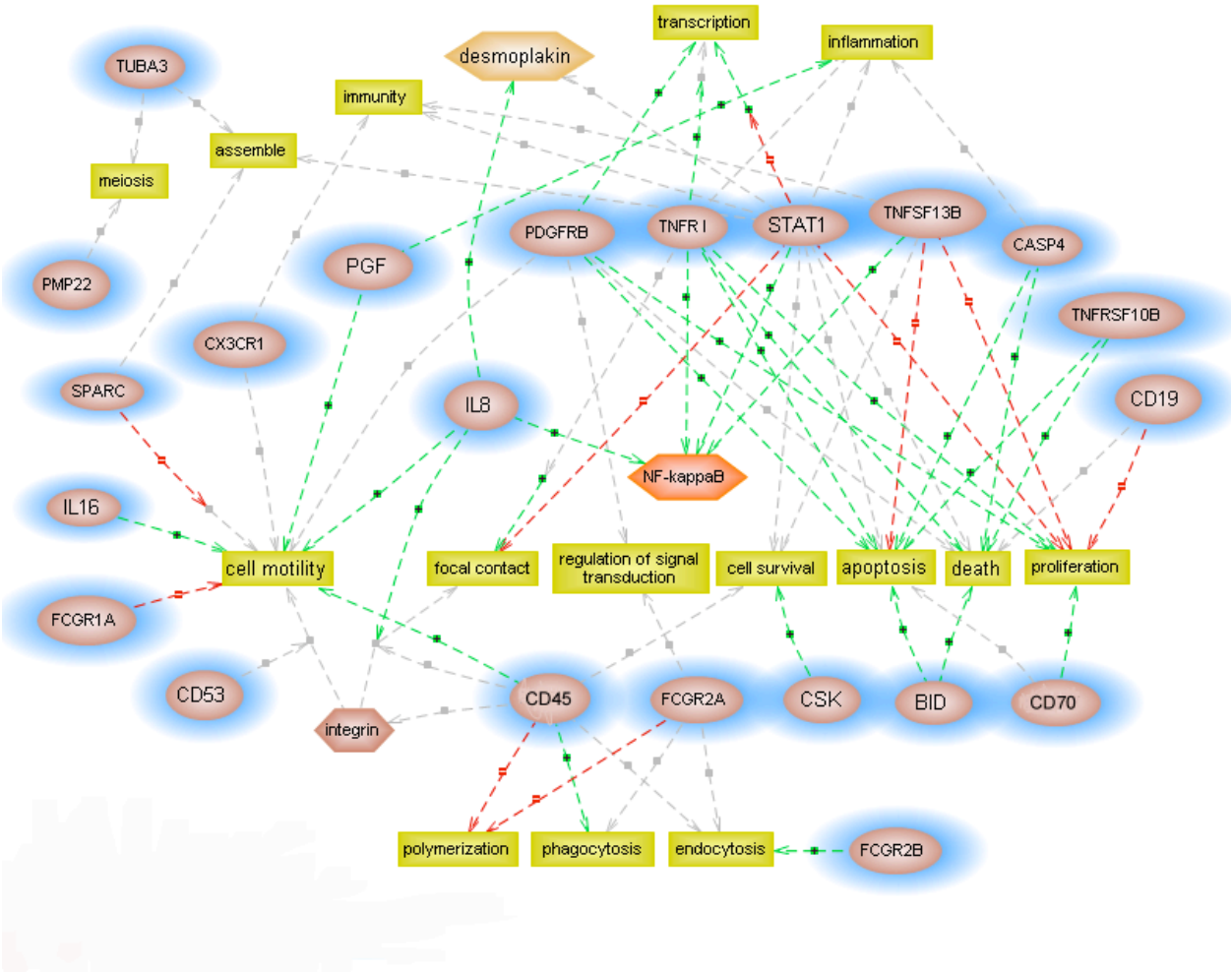


Figure 21 Network analysis of the genes that are up-regulated in both tumor-subtypes (blue halo) to identify common cellular processes (yellow boxes) and protein complexes (hexagons). Most of the processes involved are related to apoptosis or cell death (green arrow: activation, red arrow: inhibition, grey arrow: unknown influence).

Significant Enrichment Of Surface Markers Up-Regulated In Both Tumor-subtypes Related To Immune Response. Five out of the 12 genes (*TNFRSF10B*, *CD70*, *TNFR1*, *PDGFRB*, and *BAFF*) are directly related to immune response, apoptosis, and cell death and they are up-regulated in both tumor-subtypes (Figure 22). One of these, *CD70*, stands out because of its known ability to induce apoptosis and thus its potential involvement in the tumor immune response. The genes *TNFR1* and *TNFRSF10B* are both receptors which transmit the signal for activation of apoptotic processes. BAFF is known to regulate the survival of B- and T-lymphocytes. Although the function of PDGFRB is not completely understood, it is known that it also plays a role in apoptotic processes.

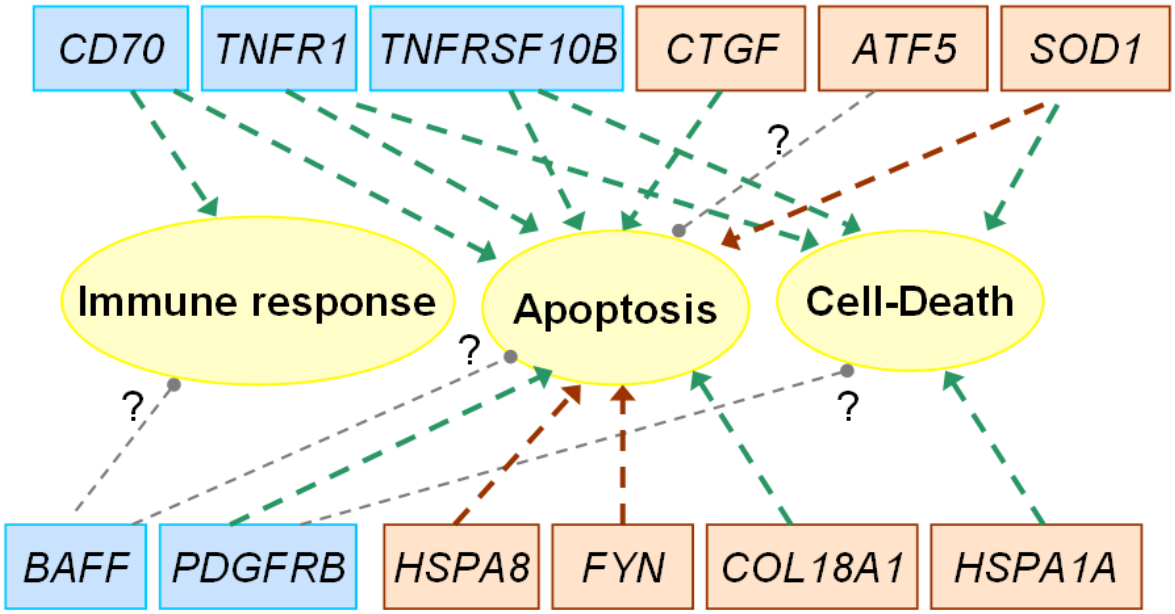


Figure 22 Schematic representation of genes equally expressed by both tumor-subtypes related to apoptotic processes (blue: up-regulated genes, red: down-regulated genes, yellow: affected processes, green arrow: activation, red arrow: inhibition, grey arrow: unknown influence).

5.4 Functional Analysis

Renal Cell Carcinoma Cell Lines Express The CD70 Ligand But Not The Receptor. In order to test whether renal cell carcinoma (RCC) cell lines express the components required for CD70-initiated apoptosis, CD70, SIVA, and CD27 expression levels were analyzed using quantitative PCR (qPCR) and immunohistochemistry (IHC).

Quantitative PCR. All RCC cell lines tested expressed the CD70 ligand, although only a negligible expression was found in the CAKI1 cell line (Table 16). In contrast, the A498 cell line showed a very prominent induction of CD70 compared to normal renal tissue. Experiments were performed in duplicates and the deviation within the standard error lies between 0.007-0.14%. In comparison to MOLT4 cells, the RCC cell lines A498 and CAKI2 show less expression of SIVA (Table 16). These experiments were performed in duplicates and the standard error lies between 0.01–0.27%.

Table 16 Expression ratios of *CD70* and *SIVA* in cell lines used determined by qPCR. *CD70* expression ratios in renal cell carcinoma (RCC) cell lines compared to normal renal tissue; *SIVA* expression ratios in RCC cell lines compared to MOLT4 cells (n.m. = not measured).

Cell Line	Relative expression of *CD70* (x-fold)	Relative expression of *SIVA* (x-fold)
A498	351.52	0.23
CAKI1	0.16	n.m.
CAKI2	1.71	0.07

Additionally, expression of *CD70, CD27*, and *SIVA* in native lymphocytes was compared to MOLT4 T-cells by qPCR (Table 17). A higher expression level for all three genes was found in native lymphocytes (Table 17). These experiments were performed in duplicates and the standard error lies between 0.05-0.23%.

Table 17 Expression ratios of *CD70, CD27*, and *SIVA* expression ratios in native lymphocytes compared to permanent MOLT4 T-cells determined by qPCR.

Gene	Relative expression (x-fold)
CD70	2.69
CD27	22149.71
SIVA	6.80

Immunohistochemistry. A confirmation at the protein level with immunohistochemistry (IHC) showed a clear signal for CD70 in the cell line A498. In both cell lines CAKI2 and CAKI1 signals could also be detected even though the staining was more heterogeneous compared to A498 cells (Figure 23). In contrast, the staining for CD27 resulted in only weak signals in all three cell lines (Figure 23).

For SIVA, a clearer signal could be detected in A498 cells whereas CAKI1 and CAKI2 cells showed weaker signals (Figure 23).

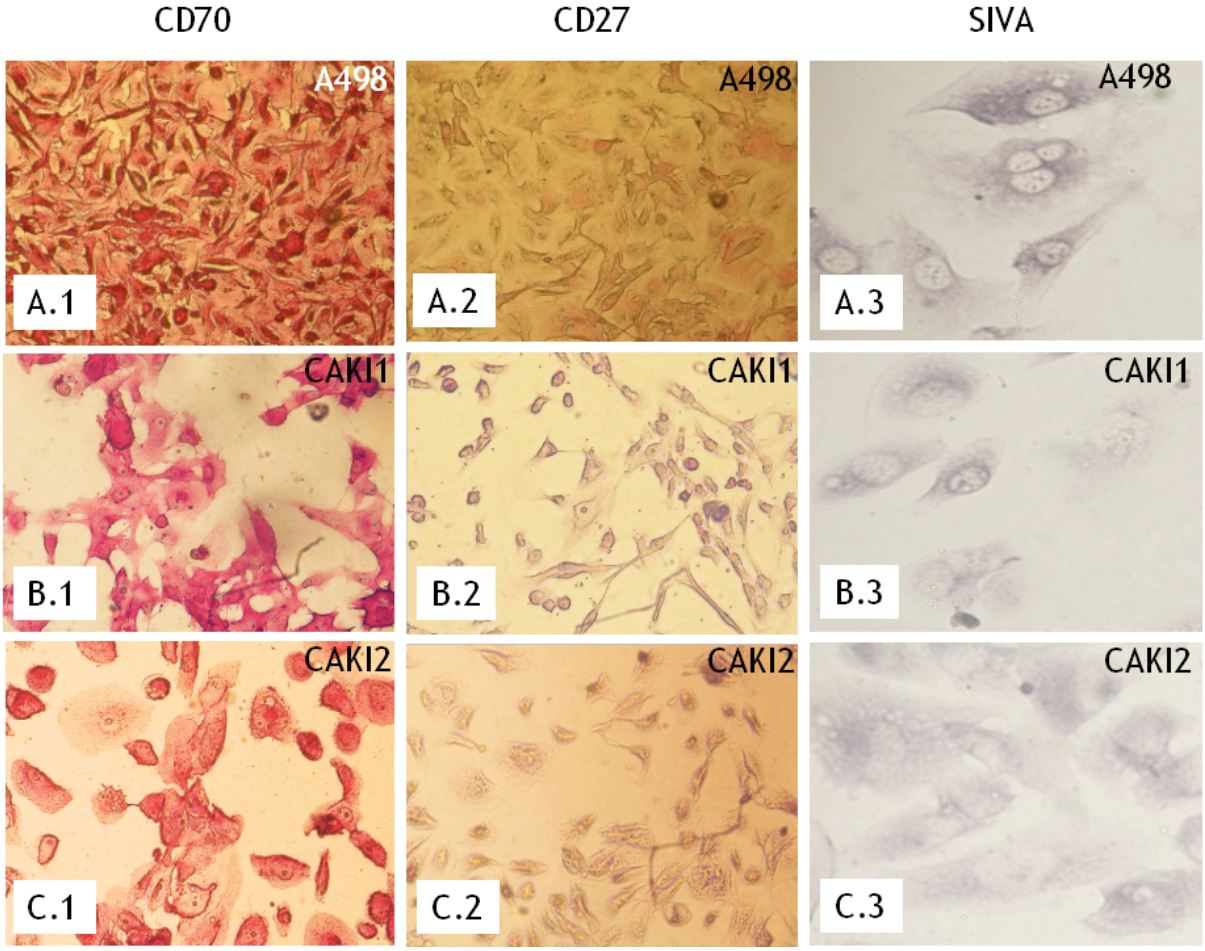


Figure 23 Immunostaining for *CD70, CD27, and SIVA* on adherent growing cell lines. **A.1**. A498 cells stained against CD70 (200x) **A.2** A498 cells stained against CD27 (200x) **A.3**. A498 cells stained against SIVA (300 x) **B.1**. CAKI1 cells stained against CD70 (200x) **B.2** CAKI1 cells stained against CD27 (200x) **B.3**. CAKI1 cells stained against SIVA (300x) **C.1**. CAKI2 cells stained against CD70 (200x) **C.2** CAKI2 cells stained against CD27 (200x) **C.3** CAKI1 cells stained against SIVA (300x) (Red color indicates presence of protein of interest).

Renal Cell Carcinoma Cells Induce Apoptosis In MOLT-4 T-cells. RCC cell lines, CAKI1, CAKI2, and A498 were co-cultured with MOLT-4 T-cells for three hours. Apoptosis was assessed in T-cells with a Caspase 3/7 assay after being separated from the adherent growing RCC cells. Two out of these three RCC cell lines (A498 and CAKI2) induced T-cell apoptosis, whereas no effect was observed with CAKI1 (Figure 24). RCC induced apoptosis in MOLT-4 T-cells was 1.31-fold for A498 (n=6) and 1.38-fold for CAKI2 (n=4; Figure 24).

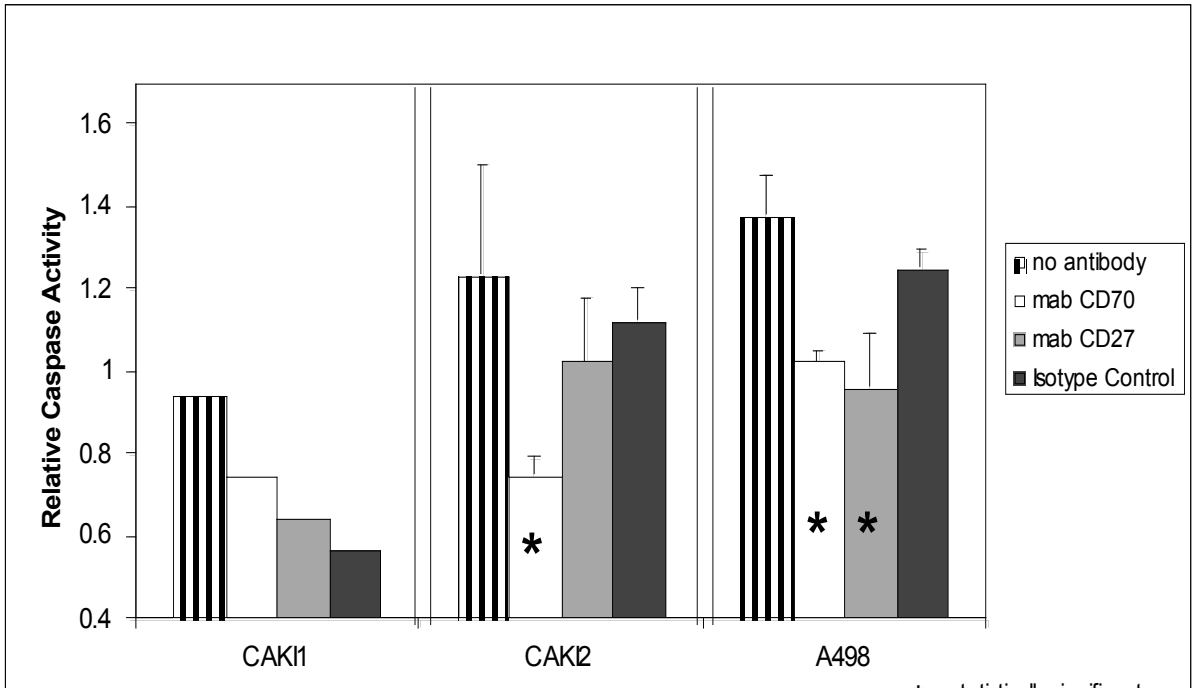


Figure 24 Apoptosis ratios of T-cells co-cultured with RCC cell lines CAKI1 (left), CAKI2 (middle) and A498 (right). The caspase activity ratio is shown relative to normal caspase activity in MOLT-4 cells in culture. (Figure legend: *vertical stripes*: no antibody added, white: anti-CD70 antibody added, grey: anti-CD27 antibody added, *black*: Isotype control added)

In order to test whether this effect is mediated by CD70 expression and transmitted via CD70/CD27 interaction, blocking experiments were performed in which anti-CD70 and anti-CD27 antibodies were added. MOLT4 T-cells co-cultured with the CD70-positive RCC cell lines A498 and CAKI2 were completely protected from induced apoptosis when anti-CD70 antibody (p-value = 0.019 for A498; p-value = 0.046 for CAKI2) or anti-CD27 antibody (p-value = 0.0014 for A498; p-value = 0.16 for CAKI2; Figure 24) was added to the cell cultures. Mouse immunoglobulin G_1 was used as a negative control and had no inhibitory effect.

Recombinant Soluble CD70 Induces Apoptosis In Lymphocyte Culture. The effect of recombinant soluble CD70 (rmsCD70) on lymphocytes was assessed to elucidate if the protein is responsible for the induced apoptosis rate. After addition of 50 ng/ml rmsCD70 to permanently growing MOLT4 T-cells, an average of 1.26-fold (n=5) T-cell apoptosis was observed. Native lymphocytes showed an average of 1.34-fold (n=2) apoptosis (Figure 25).

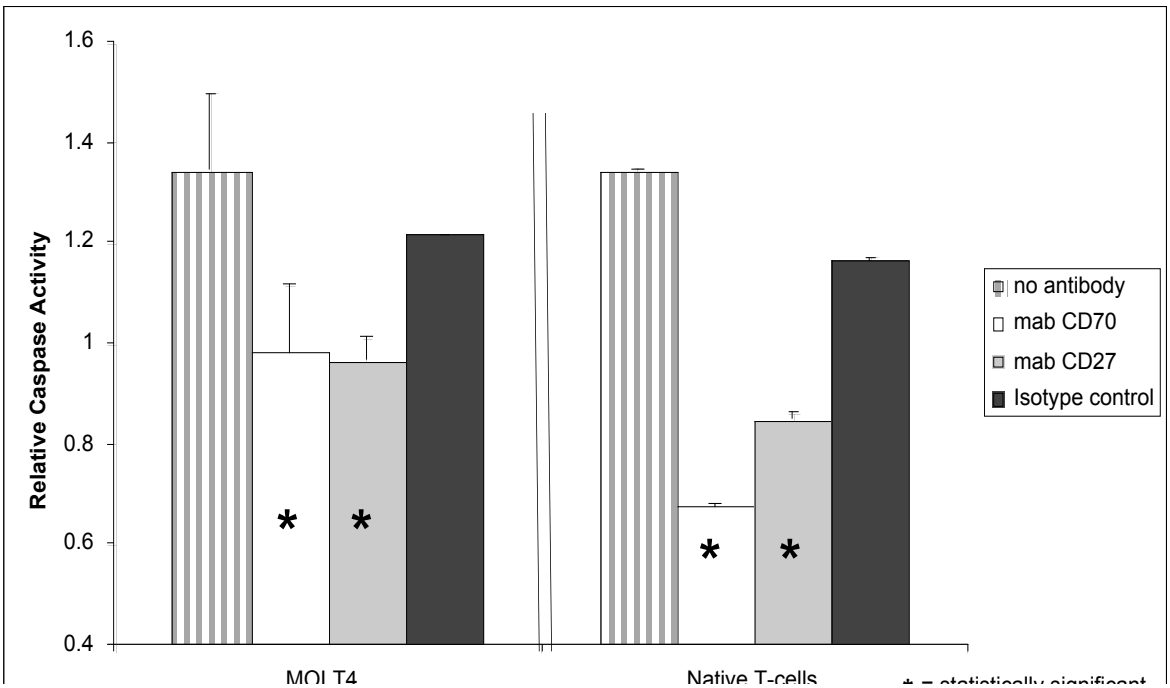


Figure 25 Effect of recombinant soluble CD70 and anti-CD70 and anti-CD27 antibodies on the apoptosis rate of MOLT4 cells (left) and native lymphocytes (right). RmsCD70 was added at a concentration of 50 ng/ml (Figure legend: *vertical stripes*: no antibody added, white: anti-CD70 antibody added, grey: anti-CD27 antibody added, *black*: Isotype control added).

In summary, the experiments with rmsCD70 and anti-CD27 and anti-CD70 antibodies revealed that CD70 has a direct effect on the apoptosis rate of lymphocytes. RmsCD70 induced apoptosis in MOLT4 T-cells was completely blocked in the presence of anti-CD27 antibody (p-value = 0.030) and in the presence of anti-CD70 antibody (p-value = 0.032; Figure 25). The induced apoptosis rate in native lymphocytes was completely blocked after adding anti-CD27 antibody (p-value = 0.011) and after adding anti-CD70 antibody (p-value = 0.005; Figure 25). In addition, the inhibitory effect of anti-CD70 antibody observed in native lymphocytes over-compensated the induced apoptosis. No inhibitory effect was observed after adding mouse immunoglobin G_1.

5.5 SUMMARY OF RESULTS

TRANSLATIONAL PROFILING. The patterns of protein expression found with SELDI-TOF technology are specific for clear cell and papillary renal cell carcinoma (ccRCC and pRCC). The peak patterns clearly distinguish the tumor-subtypes from each other and from normal renal tissue (normal). Twelve masses with a statistically significant difference in intensity were found for tumor versus corresponding normal. Twenty-two masses with a statistically significant difference in intensity were detected to be specific for ccRCC versus normal. Two peaks at 25595 Da and 30176 Da show a very high discriminative potential and are possible markers for this tumor-subtype. Forty-six masses with a statistically significant difference in intensity were found to be specific for pRCC versus normal. Of these, three peaks (25595 Da, 45888 Da, and 3339 Da) can discriminate between pRCC and normal and could serve as potential markers. Since the peak at 25595 Da has been detected for both clear cell and papillary RCC it can be considered as a general potential marker for RCC which is not discriminative between the two tumor subtypes. The peak at 45888 Da was only detected in pRCC and is absent in ccRCC. Thus it can considered as highly specific for pRCC. Fourteen masses with a statistically significant difference in intensity distinguish between ccRCC and pRCC. Two peaks at 9233 Da and 5829 Da distinguish with a high discriminative potential between ccRCC and pRCC. The respective proteins can be considered as potential markers specific for either ccRCC or pRCC. In summary, the translational analysis with SELDI-TOF technology revealed potential candidate markers for both tumor-subtypes that have to be identified and studied in more detail.

TRANSCRIPTIONAL PROFILING. The transcriptional analysis with cDNA-arrays led to the identification of potential candidate markers for both tumor-subtypes. Microarray analyses revealed 325 genes (50.1 %) to be differentially expressed in ccRCC and 602 genes (55.7%) to be differentially expressed in pRCC. Out of these differentially expressed genes those were selected that could discriminate between tumor and normal tissue. These genes for both tumor-subtypes were analyzed with quantitative PCR (qPCR) and immunohistochemistry (IHC). The gene *CD70* for ccRCC and the genes *CD37, CALB1*, *MDU1*, and *CD68* for pRCC were additionally analyzed on the mRNA-level and the expression data could be reproduced. Additionally, the specificity of CD70 was tested in IHC experiments and confirmed *CD70* as being specifically over-expressed in ccRCC compared to other RCC subtypes.

FUNCTIONAL PROFILING. Global correlation analysis of gene expression datasets showed that tumor-subtypes cluster separately. Forty-five genes are regulated equally and 13 genes are regulated differentially in ccRCC and pRCC. Functional annotation analysis reveals mechanisms enabled in both tumor-subtypes. A significant enrichment of genes that are related to an immune response are regulated in both tumor-subtypes. Among them is the gene *CD70*. The functional profiling shed light on the underlying biology of both tumor-subtypes by elucidating common processes.

FUNCTIONAL ANALYSIS OF CD70. Renal Cell Carcinoma (RCC) cell lines express the CD70 ligand but not the CD27 receptor. RCC cells induce apoptosis in MOLT-4 T-cells through CD70 expression. Recombinant soluble CD70 induces apoptosis in lymphocytes and MOLT 4 T-cells. These analyses confirmed the over-expression of *CD70* in RCC cells as being functional for the tumors.

6 DISCUSSION

The biology of renal cell carcinoma (RCC) was studied using a model system composed by the two most common RCC subtypes which, despite sharing a common cellular origin, display discrete histological and genetical patterns. In order to elucidate tumor-specific and tumor-subtype specific expression profiles, transcriptional and translational approaches have been used. These approaches were chosen because they comprise the important levels of gene and protein expression and thus provide a global look into the processes that occur in the tumor cells.

The application of these approaches led to the identification of genes and proteins that are differentially expressed in clear cell and papillary renal cell carcinoma (ccRCC and pRCC). The translational profiling resulted in specific protein patterns for each tumor-subtype. Through transcriptional profiling, potential specific marker genes for ccRCC and pRCC have been identified. Most strikingly, the over-expression of the gene *CD70* was found to be highly specific for ccRCC. Thus, *CD70* can be considered as a new marker gene for ccRCC. Finally, the gene expression data was additionally searched for groups of genes involved in similar processes. This analysis revealed a significant enrichment of genes differentially expressed in both tumor-subtypes which could be involved in an immune escape strategy of RCC. These results are particularly interesting since, despite the presence of tumor-infiltrating lymphocytes (TILs), RCC successfully manage to suppress the immune system.

Among the genes up-regulated in both tumor-subtypes was *CD70,* which has been found to be involved in the immune escape strategies of other tumors. A closer inspection of CD70 function within the tumor environment of RCC revealed its capacity to induce apoptosis in TILs and thus enable RCC to suppress the immune system. In summary, this study has not only identified new, tumor-subtype specific marker genes but has also increased our understanding of the underlying biology of RCC by identifying a possible mechanism by which RCC escapes immune recognition.

6.1 TRANSLATIONAL PROFILING

The aim of the translational profiling was to identify protein patterns specific for both ccRCC and pRCC. This was achieved by combining ProteinChip technology (SELDI-TOF: *Surface Enhanced Laser Desorption Ionization - Time of Flight*) and bioinformatic tools. The advantage of using proteomic tools for cancer analysis is the possibility to study tumor-specific expression very close to the real conditions within the cells.

Several proteomic tools are currently applied to analyze protein expression (84;85). The most widely used is the two-dimensional protein gel electrophoresis (2D-PAGE) which can display protein expression patterns to a high degree of resolution (86). However, 2D-PAGE can be time-consuming, the analysis is complicated and, compared with DNA techniques, this approach is not very sensitive. In contrast, the SELDI-TOF technology is more sensitive than 2D-PAGE, especially in the lower mass range, and it can be employed to generate protein expression patterns from whole tissue extracts. Finally, it enables the analysis of proteins at femtomole levels directly from their native sources (8, 9, 30). Previous studies applied this technique successfully for molecular cancer research (87-89).In this study, SELDI-TOF analyses of 40 tumor samples and corresponding normal renal tissue were performed in order to define tumor specific protein patterns for ccRCC and pRCC. The peak patterns clearly distinguish the tumor-subtypes from each other and from normal renal tissue.

The statistical analysis revealed several peaks with discriminative power either for normal versus tumor tissue or between both tumor-subtypes. Interestingly, several peaks were found to discriminate pRCC from both normal renal tissue and ccRCC. No such peaks were detected for ccRCC. An interpretation of this finding is highly speculative, but considering the common origin of these subtypes it could point towards evolutionary processes in the development of the RCC subtypes.

It was possible to identify the ccRCC tumor samples with a specificity of 100% and a sensitivity of 95% using bioinformatic tools. This result is consistent with two earlier published studies. Fetsch et al. investigated archival cytology material from different tumor tissues including five RCC samples of various histological subtypes (61). They were able to establish specific protein fingerprints allowing diagnosis of each tumor type in 87%. More recently, Junker et al. reported a protein set which identifies ccRCC with a sensitivity of 94.0% and specificity of 98.9% (62).

Up to now, no protein pattern specific to pRCC has been identified. Here, a set of proteins was detected that distinguishes between normal and pRCC tissue with a sensitivity of 95% and a specificity of 88%. The peak found at 45888 Da is highly specific for pRCC since it does not appear in the pattern for ccRCC. However, since the proteins found are down-regulated in the tumor tissue they are not usable as potential biomarkers. Finally, the two protein peaks (9233 Da and 5829 Da) which differ in their expression levels between ccRCC and pRCC have a discriminative potential of 79% sensitivity and 100% specificity. A further identification of these protein peaks could perhaps lead to a biomarker to distinguish the two tumor-subtypes.

As expected, more protein peaks were found to be differentially expressed between normal and tumor tissue than between ccRCC and pRCC. Fourteen protein

peaks with statistically significant differences in intensity between the tumor-subtypes were found which clearly separates them, even without knowing all of the respective proteins. Thus, the protein pattern found for pRCC shows a clear difference to the protein pattern for ccRCC.
In conclusion, the differences in protein expression detected between the tumor-subtypes are reflecting the fact that different subtypes of RCC represent independent tumor entities as shown by a variety of studies (3). For the first time, a specific protein expression pattern for pRCC was established. The patterns revealed promising candidate molecules for biomarkers that have to be studied in more detail.

6.2 TRANSCRIPTIONAL PROFILING

The transcriptional profiling studied gene expression in ccRCC and pRCC using cDNA microarrays. This technique covers the transcriptional level of expression and is very useful for the identification of more genes relevant for RCC development and progression. However, microarray data must be confirmed by array independent technologies like qPCR, which is used to quantify physiological changes in gene expression and to verify gene expression results derived from microarrays (71;90). Nevertheless, microarrays have already been applied successfully for biomarker discovery (91;92).
In general, our knowledge about differentially regulated genes in pRCC is still limited (81;82) even though genes involved in ccRCC have been identified. The most prominent finding for RCC so far is the identification of the *Von Hippel-Lindau tumor suppressor* gene (VHL) as being involved in the development of distinct types of RCC. It is located on chromosome 3p25-26 and was found to be altered in up to 75% ccRCC by mutations or hypermethylation (93). Thus, the microarray analysis carried out in this study revealed differentially expressed genes specific for either normal or tumor tissue in both tumor-subtypes. Potential candidate molecules for both tumor-subtypes could then be studied in more detail.

POTENTIAL MARKER GENES FOR CLEAR CELL RENAL CELL CARCINOMA. In general, the gene expression data found for ccRCC is consistent with previously published data. The pattern of regulations found in this study for genes such as *collagen type II, IV as well as integrin, type alpha, 1* and *5*, and *beta, type 2* were the same as seen in a study by Droz et al. (94). However, this study revealed two additional genes, *CD70* and *FOSL2,* to be differentially expressed between tumor and normal tissue in 80% or more of the samples. These two genes were thus subjected to further scrutiny with qPCR and IHC.

The discriminating potential of *FOSL2* found by microarray analysis could not be confirmed with qPCR and was only detected focally in two cases with IHC. This is not surprising given the differences in sensitivity among the techniques, especially the high sensitivity of qPCR versus microarrays. Meanwhile, the discriminative potential of *CD70* found by microarrays was confirmed by both qPCR and IHC. The over-expression was confirmed in eight of ten samples by qPCR and also IHC analyses for these ten samples showed a clear signal in ccRCC. In order to examine the specificity of *CD70*, IHC was carried out with more ccRCC samples as well as with other RCC subtypes (83). Whereas samples from chromophobe, papillary or oncocytoma showed no reactivity, in all additional ccRCC samples a strong protein expression of CD70 could be detected.

In addition, the recently described marker *CXCR4* was found by microarray experiments to be over-expressed by in ccRCC. *CXCR4* expression in ccRCC was confirmed by microarray experiments in seven out of ten tumor samples. However, it showed heterogeneous staining in IHC (95). In contrast, the IHC experiments with CD70 showed conclusive results in almost all examined ccRCC samples, whereas the other tumor-subtypes were negative. Thus, among the genes identified by microarrays, the gene *CD70* can be considered as a new, specific marker gene for ccRCC.

Although some information about *CD70* is available, the role of this gene in tumor development and progression remains unclear. It is a Type II transmembrane glycoprotein known to mediate the interaction between T-and B- lymphocytes, and natural killer-cell activation. It has also been implicated in processes like cell proliferation, signal transduction, and cell-to-cell signalling, and can also induce apoptosis by binding to its receptor CD27 (96;97). In addition, several studies have shown that *CD70* can be over-expressed in malignant lymphomas and nasopharyngeal tumors which are both associated with Epstein-Barr virus (96). More recently, CD70 has been proposed as a possible target molecule for antigen-dependent cytotoxicity in metastatic sites of RCC (98). Nevertheless, in other genome wide studies performed so far, with the exception of the study of Lenburg et al., the up-regulation of *CD70* has not been detected in ccRCC (82;99).

Given that RCC is known to be infiltrated by lymphocytes, it is tempting to speculate that *CD70* over-expression might play a role in RCC immune escape through induction of lymphocyte apoptosis. This is especially the case since Chahlavi et al. showed that the over-expression of CD70 in glioblastoma leads to T-cell death (100). Interestingly, the role of CD70/CD27 interactions in T- and B-cell activation has already led to promising treatments for cancer (97). The possible role of CD70 in ccRCC is discussed in chapter 6.4.

POTENTIAL MARKER GENES IN PAPILLARY RENAL CELL CARCINOMA. The microarray data for pRCC was compared with earlier studies. The results were consistent with those studies that had overlapping datasets. For example, the gene expressions found match previously published data for the genes *THBS2, C-Kit, GRO-1, TIMP1, TIMP2, CXCR4*, and *IGFBP6* (12;80;81;101).
Of special interest were the genes *CD37, CALB1, CD96,* and *CD68* because of their high potential to discriminate between normal and tumor tissue. A confirmation of the microarray data via qPCR showed a strong correlation for all examined genes. In order to confirm the expression patterns found independently from the microarray experiments, four separate pRCC samples that had not been analyzed on microarrays were subjected to a qPCR analysis. Again, the expression patterns found with the microarrays were confirmed. However, the over-expression of *CD37* in pRCC could not be confirmed via IHC. Due to the lack of appropriate antibodies IHC confirmation for the other three candidate molecules is still missing.
These candidates are known to be involved in several processes. CD68 could play a role in phagocytic activities of tissue macrophages, both in intracellular lysosomal metabolism and extracellular cell-cell and cell-pathogen interactions. CD96 promotes natural killer (NK) cell adhesion to target cells expressing polivirus receptor (PVR), stimulates cytotoxicity of activated NK cells, and mediates acquisition of PVR from target cells (102). CALB1 buffers cytosolic calcium and may stimulate a membrane Ca^{2+}-ATPase and a 3',5'-cyclic nucleotide phosphodiesterase. These three genes can be considered as potential marker genes for pRCC but their specificity and reliability needs to be confirmed on the protein level.

In summary, expression profiling with cDNA-arrays of both RCC subtypes led to promising candidate molecules. After confirmation with two independent methods the gene *CD70* can be considered as a new, specific marker gene for ccRCC. Furthermore, this approach demonstrates that it is crucial to combine cDNA-arrays with appropriate confirmation techniques that do not rely only on the “rnomic” level of gene expression but take into account as well the protein expression. Nevertheless, considering that one gene is not enough to characterize a tumor the lists of differentially expressed genes created by cDNA-arrays have to be studied as well from a functional point of view.

6.3 FUNCTIONAL PROFILING

The gene expression data for both tumor-subtypes still contains more information regarding functional connections between the genes found. In a functional approach this information was extracted by searching the data for genes that are involved in similar biological processes, like for example apoptosis. Even though

gene expression studies of RCC using microarray technologies have successfully identified cancer associated expression patterns and potential marker genes (99;103-105), no functional profiling of these gene expression data has been carried out for RCC so far. Therefore, functional profiling was performed to extract the biological information of the gene expressions found in both tumor-subtypes.
The aim of the functional profiling was to compare the gene expression of ccRCC and pRCC in order to find pathways and mechanisms enabled in only one or in both tumor-subtypes. First, the gene expression of both tumor-subtypes was analyzed. Using Miltenyi´s TreeRanker system clusters of interacting genes were found to be coordinately or differentially up- or down-regulated. Second, a dataset with differentially expressed genes (a total of 13 genes) between ccRCC and pRCC was identified. And third, a dataset with 45 genes regulated equally in both tumor-subtypes was found. Functional profiling revealed differences and similarities in the biology of both tumor-subtypes.

GENES DIFFERENTIALLY EXPRESSED COMPARING THE TUMOR-SUBTYPES. The first dataset analyzed contained 13 genes that are differentially expressed between both tumor-subtypes. This dataset serves to discriminate between the two RCC subtypes. *FOSL2* and *HEVIN* exhibit the most contrary expression between the examined tumor-subtypes. *FOSL2* is strongly down-regulated in ccRCC whereas *HEVIN* is down-regulated in pRCC. Unfortunately, the suppression of *FOSL2* could not be confirmed. No additional confirmation has been carried out for *HEVIN* so far.
A number of genes identified as being up-regulated in ccRCC but not in pRCC play a role in cell-cell recognition, like *VEGFA* and *VCAM1*. Interestingly, *CD40*, a gene up-regulated in ccRCC, is also involved in an immune response by regulating B-cell proliferation. An up-regulation was also found for the gene *TNFR2* that mediates most of the metabolic effects of *TNF-alpha* including blocking its apoptotic functions.
The findings that the genes *RPS7, CD151, LUMAN*, and *ATF4* are up-regulated in ccRCC but not in pRCC is congruent with previous studies that report discrete microarray patterns in RCC subtypes (12;99;105). In this study, differences in regulation between the two tumor-subtypes for *CD70, PLGF*, and *CCND1* were found. The gene *CCND1* showed a rather heterogeneous expression pattern and was not consistently expressed in all patient samples analyzed. Meanwhile, *CD70* and *PLGF* were strongly up-regulated in ccRCC but nearly unaffected in the pRCC dataset. A closer look at the induction revealed that while both genes are only slightly induced in pRCC, they are more than 20- fold up-regulated in ccRCC. These ambiguous results for *CD70* and *PLGF* might not only reflect the heterogeneity of the cell population in the examined tumor tissues, but also sample-specific

differences in gene expression. Consequently these genes were included in both the equally and differentially expressed gene datasets.

GENES EQUALLY EXPRESSED IN THE TUMOR-SUBTYPES. The 45 genes equally expressed (23 down-regulated and 22 up-regulated) by both tumor types were analyzed via functional profiling. The results for the 23 down-regulated genes showed that the majority of these genes are enzymes (ten genes) and genes involved in lipid and carbohydrate metabolism (seven genes). The functional analysis revealed their involvement in several cellular processes like cell motility, proliferation, and angiogenesis. Most importantly, several of these commonly down-regulated genes were found to be involved in mechanisms concerning apoptosis and cell death (*FYN, COL18A1, CTGF, SOD1, ATF,* and *HSPA1A*).
Most of the 22 up-regulated genes in both tumor types are surface markers. Since these markers play a key role in cell-cell communication and are crucial for adaptive and antigen-directed immunity, the analysis was constrained to identify the underlying functional relations between them. Among the genes found to be regulated are *FCGR1A*, *FCGR2*, and *CD45*. They are known to be regulators of T-cell antigen receptor signalling and could therefore be directly involved in an immune response of RCC (106). *CD19* may be involved in growth regulation of B-cells and *CD68* could play a role in phagocytic activities of tissue macrophages, both in intracellular lysosomal metabolism and extracellular cell-cell and cell-pathogen interactions. The gene *PMP22* might be involved in growth regulation whereas PDGFRB is a receptor that binds specifically to PDGFB and has a tyrosine-protein kinase activity.
Most interestingly, four of the twelve up-regulated surface markers, TNFRSF10B, CD70, TNFR1, and BAFF, belong to the tumor necrosis factor/tumor necrosis factor receptor related superfamily, a group of proteins that function as communicators between cells. Additionally, a fifth surface marker, PDGFRB, has been found to be up-regulated in both tumor-subtypes. These five proteins can mediate apoptosis or are linked directly to an immune response via their ability to regulate the reaction of lymphocytes to pathogens (107;108). Given the strong up-regulation of *CD70* in ccRCC and the accumulation of up-regulated immune-regulatory genes in RCC, it is tempting to speculate that genes belonging to the TNF receptor family could play a key role in RCC immune escape.

In summary, the approach used here provides information not only on the differences between ccRCC and pRCC, but also on the functional similarities of these two most common RCC subtypes reflecting their shared origin. The increased expression of apoptosis-inducing genes seems, at first glance, to be antithetical to

tumor survival. However, it is of special interest since tumor-infiltrating lymphocytes (TILs) are often reported for RCC. An induction of apoptosis in these cells could enable RCC to suppress the immune system. The gene *CD70* seems to have the highest potential to play a role in immune escape due to its confirmed over-expression in RCC and, its role in the immune escape strategies in other tumor types. Thus, further investigation of CD70 was undertaken to see if it is involved in the immune escape strategy of RCC by inducing apoptosis in TILs.

6.4 Functional Analysis

The aim of the functional analysis was to examine the function of *CD70* over-expression in RCC given that cancer patients, including those with RCC, are known to have impaired antitumor immune responses. It is also known that despite the presence of tumor-infiltrating lymphocytes (TILs), RCC can successfully escape immune recognition. But even though RCC is generally considered an immune-regulatory tumor only, a few mechanisms for its immune-suppression have been identified. These findings include that one way for these tumors to evade the immune system is via induction of apoptosis in T-cells through FasL expression (62;109-112).

A closer look into the CD70/CD27 pathway reveals that the interaction of CD70 with its receptor, CD27 can also lead to T-cell apoptosis, probably due to persistent stimulation (Figure 26; 113). Since CD27 lacks the death domain, the apoptotic signal is transmitted via the apoptotic protein SIVA (114). It is also known that CD70 belongs to the tumor necrosis factor family. Most notably, members of this family have central roles in adaptive and antigen-directed immunity when they coordinate the response of lymphocytes to pathogens (107).

The functional analysis of CD70 expressed by RCC cell lines or recombinant soluble CD70 (rmsCD70) showed that it can be responsible for apoptotic cell death in lymphocytes. Both tumor cell lines expressing CD70 were capable of inducing apoptosis in lymphocytes, whereas the non-expressing tumor cell line CAKI1 had no measurable apoptotic influence on the lymphocytes. Furthermore, the addition of rmsCD70 in physiological concentrations to both, permanent and native lymphocytes in culture increased the apoptosis rate significantly. The involvement of CD70 was shown by blocking experiments with antibodies against CD70 ligand and CD27 receptor.

Interestingly, RCC can induce expression of immune-suppressive mediators such as prostaglandin E2 by peripheral blood mononuclear cells (115). It has already been speculated that this, in combination with CD70 expression, may skew the immune system to a prominent humoral response or, even worse, complete immune

escape/successful immune-suppression (56). The findings of this study support this hypothesis.

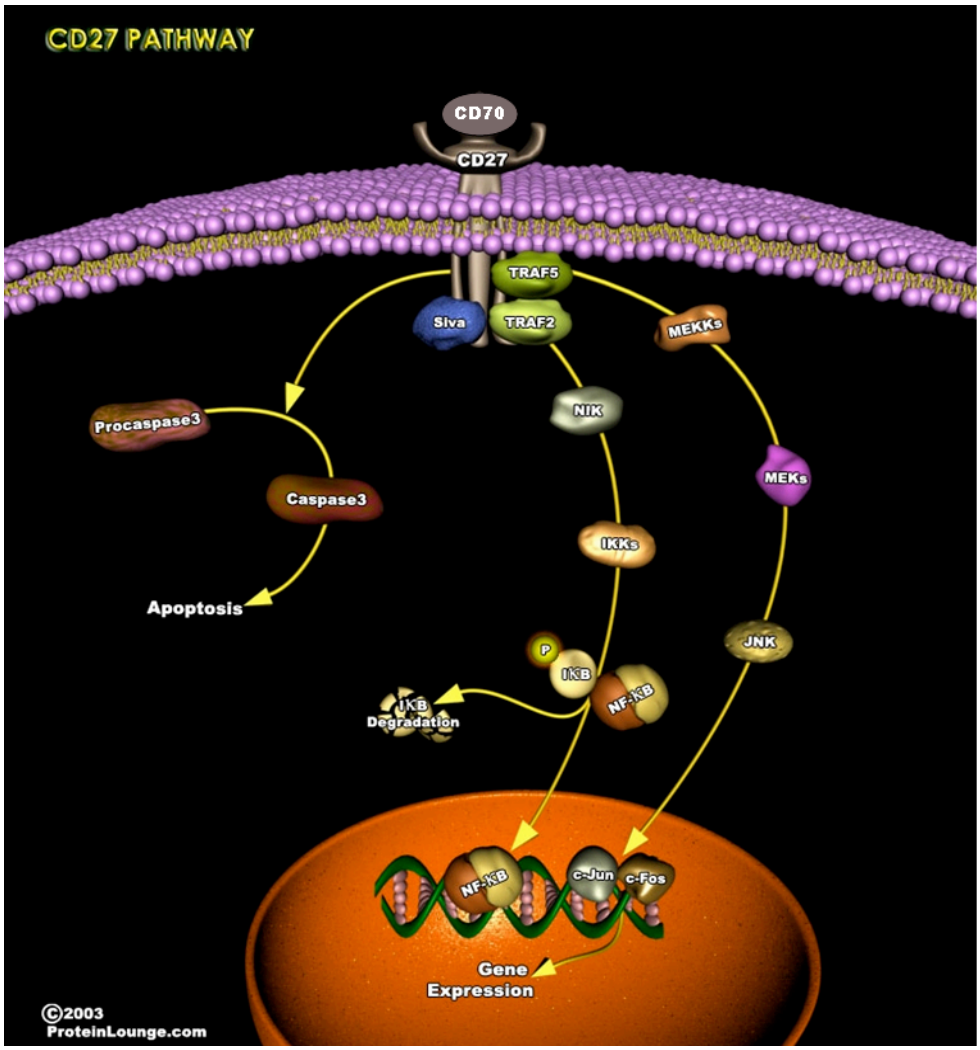


Figure 26 CD27 pathway. Binding of CD70 Ligand to CD27 receptor can lead to apoptosis as well as to proliferation (www.proteinLounge.com, modified).

In a different study the role for CD70 expression has already been examined for glioblastoma (116). CD70 expression by glioma cells leads to apoptosis of peripheral blood mononuclear cells and enhancement of the level of soluble CD27. Hence, CD70 expressed by glioma cells evoked immune inhibition rather than immune stimulation. On the other hand, a study carried out by Aulwurm et al. suggests that immune stimulatory effects of CD70 override CD70-mediated immune cell apoptosis in rodent glioma models and confer long-lasting antiglioma immunity *in vivo* (117). These differing findings suggest that the effects carried out after activating the CD70/CD27 pathway are highly complex and should be investigated in more detail. Little is known so far about possible interaction partners of CD70 and CD27 that may have regulatory functions for the pathway.

Recent data for CD70 leads to the assumption that apoptosis mediated by the CD70/CD27 pathway involves the apoptotic protein SIVA (Figure 26; 97;116). In this

study, CD27 as well as SIVA expression was shown for permanent and native lymphocytes whereas no expression was found in the permanent RCC cell lines. In addition, no CD27 expression was found in ccRCC by cDNA-microarrays or qPCR or IHC analysis. These findings point to a specific activation of the CD70/CD27 pathway by the tumor cells in TILs.

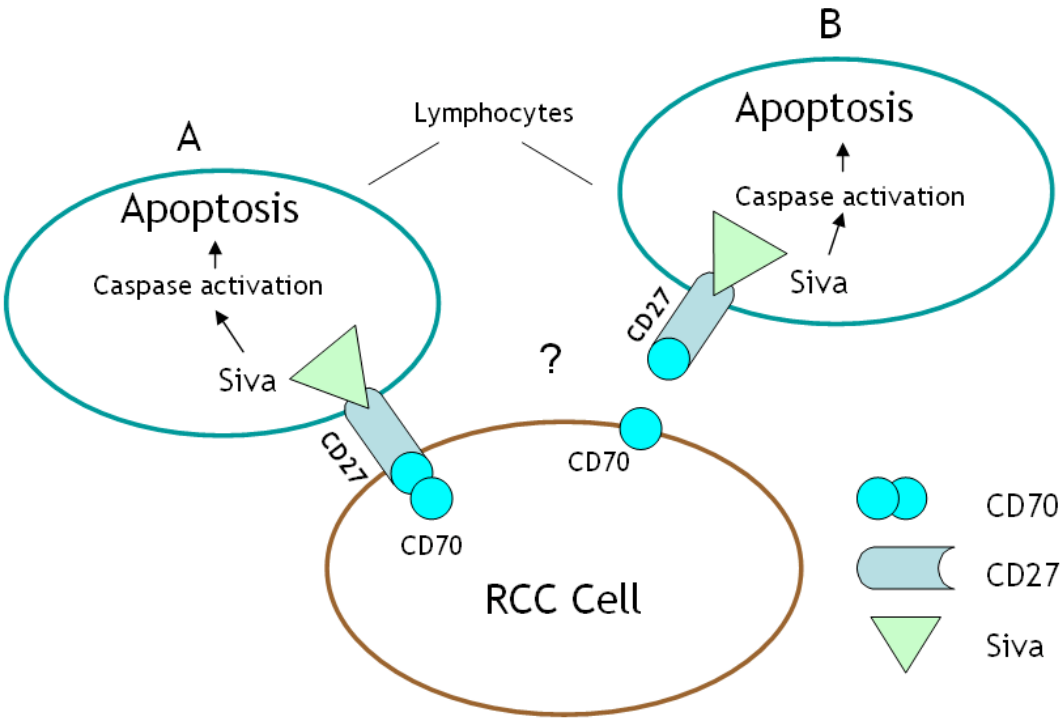


Figure 27 Schematic representation of apoptosis induction via CD70 expression in renal cell carcinoma (RCC) cells. A. Apoptosis induction through cell-cell contact. CD27 receptor is expressed by lymphocytes and CD70 ligand is membrane-bound in RCC cells. Apoptosis is induced after binding of death-domain substitute SIVA which initiates caspase activation. B. Apoptosis induction without cell-cell contact. Membrane-bound CD70 ligand is cleaved and binds to CD27 receptor. Apoptosis is induced after binding of death-domain substitute SIVA which initiates caspase activation.

However, it remains unclear how the apoptotic signal is transmitted. The experimental design of this study suggests two possible ways. One is the induction of the apoptotic signal through direct lymphocyte - RCC cell contact (Figure 27, Part A). Another possible mechanism is the cleavage and release of CD70 to the surrounding environment. No direct cell-cell contact would be necessary (Figure 27, Part B). However, from what we know it seems more likely that the cells have direct contact while transmitting the signal since the release of CD70 to the environment has not been demonstrated so far.

In conclusion, the functional analysis provides evidence for a possible mechanism used by RCC to eliminate lymphocytes and prevent an immune response via the over-expression of CD70. It was shown here that soluble CD70 as well as CD70 expressed by RCC cell lines leads to apoptosis in lymphocytes. Thus, this study identified a new, potential mechanism for RCC to successfully escape immune recognition.

7 CONCLUDING REMARKS

This study shows that the combination of transcriptional and translational profiling represents a powerful tool for the molecular dissection of cancer. The upgrade of these approaches with functional profiling also addresses functional connections between the regulations found and underlines the need of comprehensive approaches for marker gene discovery that reflect the complexity of tumor development and behavior. Most importantly, the comparative study of the model system composed by two renal cell carcinoma (RCC) subtypes sharing a common cellular origin resulted in a gain of knowledge about RCC biology and shed more light onto the processes responsible for tumor development and behavior.

Tumor-specific gene and protein regulations as well as potential tumor-specific marker genes in clear cell and papillary renal cell carcinoma (ccRCC and pRCC) were identified. The most striking discovery is the identification of the gene *CD70* as a new, highly specific marker gene for ccRCC. This gene was then further characterized regarding its function and found to be responsible for lymphocyte apoptosis. Thus, this study identified a new, potential mechanism for RCC to suppress the immune response.

In addition, this study also led to topics that need to be addressed in further studies. No possible protein interaction partners for CD70 or its receptor CD27 have been described so far. Their function in the tumors could be influenced by secondary proteins that have regulatory effects. The activation of the CD70/CD27 pathway in RCC should be confirmed in mouse models to elucidate whether this mechanism is enabled *in vivo* as well. In this context, the question of whether CD70 is released by the tumor cells or if it remains membrane-bound before binding to CD27 receptor still needs to be addressed.

However, our view into the processes involved in tumor development and tumor behavior is still restricted to one expression level at one time-point due to methodological limitations. Future investigations would be improved if the data derived from the expression approaches could be better integrated to give a more comprehensive view of all layers of regulations that characterize the tumor. This would allow also for a better understanding of tumor development and behavior and thus tumor biology.

8 DEUTSCHE KURZFASSUNG

Die Biologie von Nierenzellkarzinomen (NZK) ist bisher nur unzureichend verstanden. NZK sind die häufigsten malignen Tumoren der Niere und lassen sich in fünf Subtypen einteilen: klarzellige, papilläre und chromophobe NZK sowie Sammelgang-Karzinome und Onkozytome. Am häufigsten werden klarzellige und papilläre NZK diagnostiziert, die beide aus dem proximalen Tubulus der Niere entstehen. Trotz des gemeinsamen Ursprungs sind sie sowohl histologisch als auch genetisch eindeutig voneinander unterscheidbar und stellen somit ein optimales Untersuchungsmodell dar, um tumor-spezifische und tumorsubtyp-spezifische Muster zu erkennen. Das Ziel dieser Arbeit ist, potentielle Markergene für klarzellige und papilläre NZK zu identifizieren, ihre Spezifität und Relevanz für den Tumor zu bestimmen und damit das Tumorverhalten und die Tumorentstehung von NZK besser zu charakterisieren.

Der hierfür verwendete Ansatz bezieht sowohl die translationale als auch die transkriptionale Ebene ein und gewährleistet somit eine umfassende Analyse der Protein- und Genexpression beider Tumorsubtypen. Auf translationaler Ebene wurden mit Hilfe von SELDI-TOF Technologie *(Surface Enhanced Laser Desorption Ionisation – Time of Flight)* spezifische Proteinmuster für beide Tumorsubtypen erstellt. Erstmalig konnten spezifische Regulationen des Proteoms für papilläre NZK identifiziert werden. Auf transkriptionaler Ebene wurden zahlreiche differentiell exprimierte Gene mittels *cDNA-microarrays* detektiert. Für ausgewählte Gene, deren differentielle Expression in NZK bisher unbekannt war, erfolgte eine Validierung auf RNA- und Proteinebene. Hier konnte das Gen *CD70* als überexprimiert in klarzelligen NZK identifiziert werden und ist ein neues, spezifisches Markergen für diesen Tumorsubtyp. Die Genexpressionsmuster beider Tumorsubtypen wurden weiterhin einer bioinformatorischen Analyse unterzogen, um biologische Zusammenhänge in der Funktion der regulierten Gene zu detektieren. Es wurde eine Gruppe von Genen identifiziert, deren Mitglieder apoptotische Prozesse induzieren können. Diese Gene sind sowohl in klarzelligen als auch in papillären NZK gleichermaßen reguliert, jedoch scheint die Induktion von Apoptose auf den ersten Blick antithetisch zum Tumorverhalten zu sein. Eine Induktion von Apoptose in den tumorinfiltrierenden Lymphozyten, die sehr häufig in NZK zu finden sind, würde es aber den Tumoren ermöglichen, das humane Immunsystem zu unterdrücken. Zu den apoptose-induzierenden Genen in dieser Gruppe gehört auch das Gen *CD70,* dessen Funktion mit Hilfe von Zellkulturexperimenten untersucht wurde. Diese Experimente zeigten, dass CD70 Apoptose in Lymphozyten induziert. Die Induktion von Apoptose durch Überexpression von *CD70* in NZK ist ein potentieller, bisher unbekannter Mechanismus, mit dem NZK dem humanen Immunsystem entkommen können.

9 REFERENCES

9.1 LIST OF OWN PUBLICATIONS

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10 EQUIPMENT AND CHEMICALS

10.1 EQUIPMENT

Translational Profiling

Determination of protein concentration

- Halfmicrocuvettes, Sarstedt

SELDI TOF MS Technology

- ProteinChip System 400

Transcriptional Profiling

RNA isolation and RNA amplification

- Bioanalyzer 2100, Agilent Technologies
- Cryostat, CM 1850, Leica
- Peltier Thermal Cycler PTC-200, MJ Research
- DNA120 Speed Vac, Thermo Savant

Microarrays

- PIQOR™ Immuno/Onco-Chip, human, antisense, Miltenyi Biotec GmbH
- PIQOR™ Immunology Chip, human, antisense, Miltenyi Biotec GmbH
- GenePix Scanner 4000B, Axon
- ScanArray 4000 Lite, Perkin Elmer
- Hybridization chamber, PIQOR™ HybChamb, Miltenyi Biotec GmbH
- GeneTAC hybridization station, Perkin Elmer
- ImaGene software version 4.1, BioDiscovery
- Wash container, Milian Laboratories supplies

Quantitative PCR

- LightCycler, Roche
- LightCyclerCapillaries, Roche

Immunohistochemistry

- Cryostat, CM 1850, Leica

Functional Analysis

Cell Culture

- Culture Flasks 7 cm^2, 25 cm^2 and 75 cm^2, Greiner Bio-One GmbH
- CO_2-Incubator Typ BB 6000, Heraeus sepatech
- Invers-Microscope, Telaval 3, Zeiss
- 0 Series (PCS 4000 TOF – MS Personal), Ciphergen
- CM10 Chip, Ciphergen

Apoptosis

- SpectraMax, Gemini, Molecular Devices
- FIA-Plate, Black, 96 well plates, Greiner Bio-One GmbH

Centrifuges and Vortexer

- Millipore Microcentrifuge MC-13, Amincon Bioseparation
- C-1200 Mini Centrifuge, National Labnet Co
- Appligene, Oncor
- Universal 30 RF, Hettich
- Megafuge 1.0, Heraeus sepatech
- MS1 Minishaker, IKA
- REAX top, Heidolph
- Biofuge Stratos, Heraeus

Other Equipment and Consumables

- Tubes, different types, Sarstedt and Eppendorf
- Tips, unsealed and sealed, 10 µl, 100 µl, 200 µl and 1000 µl, Gilson and Biozym
- Falcon tubes 15 ml and 50 ml, Greiner Bio One GmbH
- Scale BP 61, Sartorius
- WPA biowave S 2100 Diode Array Spectrophotometer, Biochrom AG
- Waterbath, Memmert

10.2 CHEMICALS

Translational Profiling

Cell lysis and protein extraction

- Sodium phosphate, Merck
- EDTA, Sigma
- Magnesiumchloride, Sigma
- ß-2-Mercaptoethanol, Sigma
- CHAPS, Roche
- Leupeptin, Serva
- PMSF, Roth

Determination of protein concentration with Bradford

- Bradford Staining solution, Bio Rad

SELDI

Energy absorbing Matrix:

- Sinapic Acid, SPA, Ciphergen

CM10 Chip:

- ACN, Aldrich
- trifluoroacetic acid, Aldrich

Transcriptional Profiling

RNA Isolation and Amplification

- E.coli DNA Ligase, Gibco BRL
- DNA Polymerase I, Gibco BRL
- Ribonuclease H, Gibco BRL
- Superscript II RNase H-Reverse Transcriptase including 5 x First Strand Buffer, 0.1 M DTT, reverse transcriptase, Invitrogen
- MEGAscript T7 Kit, Ambion
- QIAquick PCR Purification Kit, Qiagen
- RNeasy Mini Kit, Qiagen
- Hexanucleotide Mix (10x), Roche Diagnostics

Microarrays

- Superscript™II RNase H-ReverseTranscriptase (RT) including 5× First Strand Buffer and 0.1 M DTT, Invitrogen
- 100 mM dNTP set, Invitrogen
- OligoDT and random hexamers, Birch-Hirschfeld, Friedrich-Schiller University, Jena
- Ribonuclease H (RNaseH, 2.2 U/µL), Invitrogen
- FluoroLink™ Cy3-dCTP, GE Healthcare
- FluoroLink™ Cy5-dCTP, GE Healthcare
- CyScribe GFX, GE Healthcare
- Ethanol (EtOH), Merck KGaA
- Prehybridization solution, Miltenyi Biotec GmbH
- 2x hybridization solution, Miltenyi Biotec GmbH
- QiaQuick, Qiagen

Quantitative PCR

- SuperScript™II Reverse Transcriptase, Invitrogen
- Random hexamer primers, Birch-Hirschfeld, Friedrich-Schiller-University
- QuantiTect Primer Assay, Qiagen
- QuantiTect SYBRGreen PCR-Kit, Qiagen

Immunohistochemistry

- Acetone, J.T. Baker
- Sodium azide. Sigma

- Biotin blocking system, DAKO kit 5005 (containing biotin and Avidin-alkaline-phosphatase)
- Haemalaun solution, Merck
- Tween 20, Roche

Functional Analysis

Cell Culture

- Trypsin/EDTA-Solution, Biochrom AG
- Lymphocyte separation medium, PAA Laboratories GmbH
- Phytohemagglutinin A (PHA-L); Biochrom AG
- Recombinant soluble rmsCD70, Alexsis Biochemicals
- PBS, Gibco

Media

- DULBECCO´S MEM (1x), Biochrom AG
- RPMI 1640, Invitrogen
- Fetal Bovine Serum, Serum Med, Biochrom AG
- Amnio Max™ C-100 Basal Medium, GIBCO BRL

Apoptosis

- APO-One™ Homogeneous Caspase-3/7 Assay, Promega Madison

Antibodies

- Mouse monoclonal anti-human Anti-CD70 antibody, Ancell™
- Mouse monoclonal anti-human Anti-CD27 antibody, Ancell™
- Mouse polyclonal anti-human anti- SIVA antibody, Abnova, Taiwan
- Mouse immunoglobulin G_1, Ancell™
- Recombinant soluble CD70, Alexsis Biochemicals

11 LIST OF TABLES AND FIGURES

11.1 LIST OF TABLES

11.2 LIST OF FIGURES

12 APPENDICES

Appendix I: Results of CGH-Analyses

A. Papillary renal cell carcinoma

Patient	CGH-Analysis	Patient	CGH-Analysis
1	dim(y), enh(7,17)	14	enh(3,7,16q,17), dim(Y)
2	dim(8p11pter, Xp, Y),	15	enh(3,7,12,16,17,Xp)
3	dim(1p,20,y), enh(17)	16	enh(3,7,12), dim(Y)
4	enh(7,12,17)	17	enh(7), dim(Y)
5	enh(3q,7)	18	enh(7, 12), dim(y)
6	dim(9q22qter,17p), enh(8p12qter, 11q14q23,17q)	19	dim(14q22pter), enh(7,12,13,17)
7	enh(7)	20	dim(5q,10q24), enh(7,12,17)
8	enh(3p13qter,7)	21	enh(7,16,17), dim(Y)
9	enh(3q,7,16,17,20)	22	enh(3,4,5q,7q,12q,14,15,16q,20)
10	enh(7,8,17)	23	enh(16,17), dim(X)
11	dim(y); enh(3,7,10,16,17)	24	enh(3q,7,17q23qter)
12	enh(3, 7), dim (11q13qter)	25	dim(3p12pter), enh(4q22q28), dim(Y)
13	enh(7)	26	enh(7,17), dim(Y)

B. Clear cell renal cell carcinoma

Patient	CGH-Analysis
1	dim(3)
2	dim(3p21pter,8p,14q21q24), enh(5q21qter)
3	dim(3p13pter), enh(5q,7)
4	dim(3p,4q13q28,7q,10q22,14q13qter,16q17p), enh(2q32pter,5q31qter,6q,13q22qter)
5	dim(1p34qter,2p22pter,3,4,6,8,9,13,14,15,18q,x), enh(16q21pter,19,20)
6	dim(3p), enh(4, 5, 13, 21)
7	dim(3p13pter,14,17,20), enh(2,21)
8	dim(3p12pter,14,15,17,20,y), enh(2,7,11,12,21)
9	dim(3p13pter, 10q23qter)
10	dim(3p14p24,8p,9q21qter,14,17,18,y), enh(8q,9q21pter)
11	dim(3p,8p)
12	dim(3,8,13,14,18)
13	enh(5q23pter), dim(3p14p22)
14	dim(3p14pter)
15	dim(3p21pter,14q,18q,y); enh(5,7)
16	dim(3p13,9q17p), enh(13q21q31)
17	dim(3p21pter,14q21qter,20,22q,y), enh(4p13q28,5p23q)
18	dim(3q21pter,4,6q,9,10,14,y); enh(6q,7,12,16,17,20,22)
19	dim(3p?,8p), enh(5q22qter)
20	dim(3p14pter,9q,14q24qter); enh(5,7,12)
21	dim(1p,3,6,9,11,14); enh(1q)
22	dim(3p14pter; 9q31qter,14); enh(5,7,12)
23	dim(3p13pter,9q22qter,14q,15q,18); enh(5q33qter,20)
24	dim(3p21pter,9,14,15,22,y): enh(4,5,6q,7)
25	dim(3p14pter,8p,14q11q24,17p), enh(5q33qter)
26	dim (3p21pter)
27	dim(3p13pter, 14) enh(5)
28	dim(3p13, 9q17p), enh(13q21q31)
29	dim(2q33, 3pter21, 4, 9, 13, 14,18q), enh(5p, 7, 17q, 20)
30	dim(3p14pter, 8p, 14q21qter, 18), enh(3q25qter, 4p, 4q31qter, 5, 7, 8q, 12)
31	n.m

Appendix II: Ratio List of All Genes Present On the Microarrays

A: Clear Cell Renal Cell Carcinoma

Ratio list of all genes present on the microarray Each gene is annotated with gene name(s) and corresponding SwissProt or Unigene numbers. In addition the respective experiments are indicated. (tumor: Cy5 labelled; normal tissue: Cy3 labelled). For each gene the normalized Cy5/Cy3 ratio (representing the mean of two corresponding spots per gene) is indicated. If a ratio is shown for a certain genen in the gene list, this indicates that a more than two-fold signal intensity above the average signal intensities of the background in at least one of the two channels (Cy3 or Cy5) could be observed. No ratio (-) indicates, that the signal intensities of the respective gene did not meet the requirements mentioned above and thus could not be reliable detected in that particular experiment.

Gene name	UniGene	266	271	275	277	333	493	258	261	269	274
ABR	Hs.118021	-	-	-	-	-	-	-	-	-	-
AC15	Hs.166563	0.96	0.98	0.91	1.02	1.08	0.4	0.72	0.81	0.88	0.62
ACTA2	Hs.195851	1.44	0.51	1.34	3.25	0.32	1.57	0.2	2.46	1.32	1.76
AF6	Hs.100469	-	-	1.49	1.91	-	-	-	-	-	-
AGRIN	Hs.273330	0.73	0.77	1.11	0.4	0.49	0.87	0.86	0.86	0.67	1
AGTRL1	Hs.9305	1.22	-	-	-	-	-	-	-	-	-
ALCAM	Hs.10247	0.86	1.12	-	0.9	1.64	0.66	0.43	0.61	0.41	-
AMP	Hs.61418	0.73	1.04	-	0.92	1.14	1.06	0.79	1.1	0.74	0.87
ANPEP	Hs.1239	0.1	0.32	1.28	0.06	0.01	0.92	0.09	0.39	0.38	0.7
AP1	Hs.78465	0.66	0.89	0.81	-	0.64	1.11	1.02	0.8	1.26	0.7
APC	Hs.75081	2.33	1.35	1.18	1.15	0.66	0.56	0.79	0.93	1.17	0.63
APRIL	Hs.54673	0.47	1.8	0.81	0.73	0.73	1.48	1.17	0.85	0.44	0.44
ASB-1	Hs.153489	-	-	-	-	-	1.16	0.51	-	-	-
ASB-3	Hs.9893	1.48	-	-	-	-	-	1.53	-	-	-
ATF1:	Hs.36908	-	-	-	-	-	-	-	-	-	0.91
ATF3	Hs.460	2.6	-	-	-	-	-	6.74	-	-	-
ATF4	Hs.181243	1.39	1.69	1.51	1.74	1.74	1.25	1.09	1.37	0.76	1.06
ATF5	Hs.9754	0.55	0.64	0.88	0.37	0.82	1.19	0.56	0.76	1	0.65
ATF6	Hs.5813	0.95	0.94	0.73	0.77	0.73	0.8	0.75	0.67	0.82	0.68
BACH1	Hs.154276	1.58	0.87	-	-	-	0.56	1.56	0.8	1.14	0.89
BAD	Hs.76366	0.53	1.24	1.26	0.52	0.7	1.55	-	0.36	0.76	0.84
BAFF	Hs.270737	2.32	2.02	0.79	6.22	-	1.17	3.94	4.16	2.95	4.61
BAMACAN	Hs.24485	0.99	0.91	1.09	0.64	0.36	0.81	0.81	0.92	0.61	0.53
BARD1	Hs.54089	0.92	0.89	0.96	0.94	-	0.76	0.79	0.71	0.44	0.52
BAX	Hs.159428	0.85	0.98	1.03	0.98	0.74	1.42	1.08	1.82	1.29	1.76
BCL10	Hs.193516	-	1.49	-	-	-	-	-	-	-	-
BCL2	Hs.79241	-	1.37	-	1.29	-	-	1.61	1.24	-	-
BCL2A1	Hs.227817	-	0.85	-	-	-	1.28	0.92	-	0.58	-
BCL2L1	Hs.305890	0.64	1.18	0.6	0.22	1.27	0.73	0.57	0.65	-	0.75
BCL2L2	Hs.75244	1.26	0.92	-	-	-	-	-	0.75	-	-
BCL3	Hs.31210	1.54	-	-	-	-	-	-	-	-	-
BID	Hs.172894	1.43	1.59	1.12	1.75	-	1.27	1.18	1.7	1.93	2.4
BIGLYCAN	Hs.821	2.27	1.41	0.59	0.69	-	0.85	1.58	4.25	2.34	0.5
BIK	Hs.155419	-	-	-	-	-	-	-	-	-	-
BIP	Hs.75410	0.65	0.66	0.95	1.22	1.01	0.73	1.2	1	0.81	0.91
BMP1	Hs.1274	1.16	0.48	0.73	1.23	-	0.8	1.71	1.48	1.06	3.71
BMP2	Hs.73853	0.82	0.34	0.86	0.43	0.32	0.78	0.64	0.93	0.37	0.35
BMP4	Hs.68879	0.87	-	-	-	-	-	-	-	-	-
BMP6	Hs.285671	1.79	-	-	-	-	-	0.17	-	-	-
BMP8	Hs.99948	-	3.06	-	-	-	-	-	-	-	-
BPGF1-Q6	Hs.77266	1.68	0.82	1.1	0.96	1.95	0.8	0.87	1.25	1.25	2.76
BRCA1	Hs.194143	-	-	-	2.32	-	-	1.8	-	-	-
BSG	Hs.74631	0.31	0.91	1.4	0.69	3.72	1.62	0.59	0.85	1.33	0.69
BST1	Hs.169998	0.54	1.08	0.85	0.46	-	0.91	-	0.62	0.54	0.45
C3AR1	Hs.155935	1.39	1.95	0.85	2.13	0.74	1.08	2.29	1.23	1.92	3.4
CALB1	Hs.65425	-	-	-	0.0032	0.00765	-	0.0027	0.00315	-	0.00
CANPX	Hs.169172	-	-	-	-	-	-	1.07	-	-	-
CASP2	Hs.108131	0.65	1.02	-	-	0.7	1.51	-	0.91	-	0.78
CASP4_HUMAN	Hs.74122	1.41	1.16	1.05	2.93	1.44	1.22	2.13	0.96	2.11	2.51
CASP7	Hs.9216	1.38	1.32	1.43	1.08	-	0.89	1.42	0.82	1.23	-
CASP8	Hs.381231	1.51	1.21	0.93	0.84	-	0.77	1.66	1.75	3.28	2.46
CASP9	Hs.100641	0.72	-	-	-	-	-	-	-	-	-
CBP	Hs.270	0.44	1.07	-	-	3.92	1.38	1.38	1.03	-	-
CCNC	Hs.118442	0.89	0.36	0.71	0.5	0.95	0.76	0.62	0.33	0.79	0.75
CCND1	Hs.82932	2.75	15.16	37.07	3.04	0.86	1.41	10.15	2.57	3.09	0.93
CCND3	Hs.83173	1.5	1.18	-	1.41	-	1.13	0.84	0.61	0.37	0.79
CCNF_2	Hs.1973	2.86	-	0.45	-	-	-	0.42	1.36	0.35	-
CCNG2	Hs.429880	1.36	2.7	0.9	0.5	2.26	0.86	0.89	0.79	-	0.7
CCNH	Hs.514	0.8	0.86	0.68	0.51	0.91	1	0.65	0.62	0.52	0.84
CCR1	Hs.301921	1.73	2.12	-	-	-	-	0.4	-	-	-
CCR10	Hs.278446	0.58	0.73	0.97	0.42	0.42	1.33	0.69	0.74	0.58	0.53
CCR5	Hs.54443	0.68	0.89	0.94	0.59	1.26	0.85	0.81	1.14	0.68	0.9

Gene name	UniGene	266	271	275	277	333	493	258	261	269	274
CCR6	Hs.46468	-	-	-	-	-	-	2.23	-	-	-
CD14	Hs.75627	3.19	3.27	0.77	4.66	1.48	1.33	2.85	2.94	3.66	5.9
CD151	Hs.75564	0.78	1.09	0.93	1.26	1.09	1.41	1.26	1.56	1.26	2.56
CD19	Hs.96023	2.88	3.15	0.77	4	1.2	1.36	3.24	2.54	3.78	6.17
CD2:	Hs.89476	0.49	3.87	0.59	11.78	-	1.58	10.23	2.96	1.31	1.67
CD24	Hs.381003	0.46	-	2.96	3.15	0.71	0.85	2.04	-	2.7	3.61
CD33	Hs.83731	1.79	1.35	-	-	-	0.98	-	-	0.94	-
CD34	Hs.374990	5.94	1.01	1.69	0.64	0.78	0.96	1.14	3.28	-	-
CD36	Hs.75613	39.79	22.44	9.6	-	1.21	0.48	10.92	49.23	2.71	3.69
CD37	Hs.153053	0.59	1.25	0.67	0.64	0.46	1.79	1.23	1.35	0.66	0.69
CD39	Hs.205353	11.53	4.42	1.03	3.81	1.69	0.65	2.16	8.59	2.69	4.54
CD3D.	Hs.95327	0.35	1.08	0.42	0.56	-	2.41	1.97	0.3	0.48	0.41
CD3E	Hs.3003	1	-	-	-	-	-	-	-	-	1.22
CD4	Hs.17483	1.8	1.96	0.96	1.27	-	0.8	5.57	2.64	2.34	2.09
CD45_EX29-31	Hs.170121	0.9	2.32	-	3.54	-	0.7	3.88	1.21	1.31	1.26
CD47	Hs.82685	0.97	0.9	1.01	0.89	1.1	1.22	1.22	1	0.85	1.81
CD48	Hs.901	0.63	3.8	0.51	9.87	-	1.7	5.39	7.61	1.27	3.34
CD52	Hs.276770	0.47	1.43	0.62	4.46	1.05	2.84	5.21	3.1	0.71	3.48
CD53	Hs.82212	1.93	3.99	0.86	6.58	1.86	1.3	6.15	6.39	3.08	7.38
CD58	Hs.75626	0.94	1.19	0.64	0.88	0.67	1.45	1.73	0.81	0.65	0.66
CD59_HUMAN	Hs.278573	0.9	0.87	0.77	1.03	3.39	1.29	0.93	1.05	0.75	0.47
CD63	Hs.433996	0.63	0.91	1.84	0.83	1.98	1.22	1.23	1.14	1.31	1.32
CD68.	Hs.246381	2.19	3.89	2.75	2.14	-	1.08	2.18	2.39	2.38	4.29
CD72	Hs.116481	-	2.45	-	0.77	-	0.71	-	-	-	-
CD74.	Hs.84298	1.7	2.99	1.56	2.64	1.45	1.27	2.17	3.26	2.4	2.52
CD79A	Hs.79630	0.12	-	-	-	-	1.66	-	-	-	-
CD79B	Hs.89575	0.77	0.66	1.2	-	-	1.69	3.74	-	-	-
CD83	Hs.79197	0.63	-	-	-	2.12	-	0.86	-	-	-
CD86	Hs.27954	-	-	-	-	-	0.92	-	-	-	-
CD8A	Hs.85258	-	0.58	-	-	-	0.84	-	-	-	-
CD8B	Hs.2299	-	-	-	-	-	1.02	-	-	-	-
CD9	Hs.1244	0.78	2.06	1.15	1.06	2.18	2.18	0.84	0.9	0.48	0.75
CD97	Hs.3107	1.17	1.96	0.87	3.05	-	1.32	2.04	1.51	1.56	2.23
CDH5	Hs.76206	7.48	1.43	2.94	1.1	0.89	0.57	1.47	3.11	0.94	0.68
CDKN1A	Hs.179665	2.02	0.7	0.53	0.25	-	0.68	0.6	0.55	-	0.35
CDKN1B)	Hs.238990	1.58	1.93	1.06	1.05	0.88	0.78	0.71	1.13	0.8	-
CEBPB	Hs.99029	1.91	0.69	0.57	1.8	-	1.19	2.32	1.8	2	3.32
CEBPG	Hs.2227	1.46	-	0.61	-	-	1.09	0.6	0.72	0.73	1.12
CISH6	Hs.169836	2.44	-	-	-	-	-	-	2.29	-	-
CLARP	Hs.195175	1.21	0.95	0.98	0.68	0.29	1.11	1.11	0.89	0.61	0.64
C-MAF	Hs.30250	-	-	-	-	-	-	-	5.89	-	-
COL12A1	Hs.101302	0.64	0.65	0.85	0.71	0.84	0.58	0.52	0.61	0.6	0.74
COL15A1	Hs.83164	9.88	0.39	0.53	-	-	0.49	3.16	2.33	2.88	1.6
COL16A1	Hs.26208	0.1	-	-	-	-	-	-	-	-	-
COL18A1_1	Hs.78409	0.74	0.33	0.8	0.4	0.28	0.73	0.63	0.83	0.38	0.43
COL18A1_2	Hs.78409	0.62	1.36	0.92	0.67	1.09	1.29	0.84	0.81	0.66	0.52
COL1A1	Hs.172928	0.77	0.17	0.09	5.09	1.36	0.55	1.07	1.81	9.17	4.73
COL1A2	Hs.179573	1.12	0.26	-	3.01	-	0.43	1.01	1.05	4.81	3.28
COL3A1	Hs.119571	0.99	-	0.17	3.68	3.27	0.55	1.15	1.36	3.69	4.22
COL4A1	Hs.119129	6.36	0.33	1.47	2.52	1.17	0.48	3.53	3.96	3.02	2.74
COL4A2	Hs.75617	3.26	0.43	1.43	2.08	0.78	0.8	2.37	2.62	1.53	1.81
COL4A3	Hs.530	0.05	-	-	-	-	-	-	-	-	-
COL5A1	Hs.146428	0.91	-	-	-	-	0.53	-	-	3.56	-
COL5A2	Hs.82985	2.84	0.6	1.52	2.4	1.57	0.39	1.78	2.1	3.38	2.05
COL6A1	Hs.108885	0.95	-	0.85	0.57	3.18	0.88	-	0.4	-	0.66
COL6A2	Hs.159263	1.85	0.7	1.38	3.5	-	0.65	1.35	1.24	2.51	2.22
COL7A1	Hs.1640	0.32	0.03	-	-	-	-	-	-	-	-
COL8A1	Hs.114599	0.7	0.62	1.65	0.84	0.59	1.63	1.27	2.98	0.9	-
COL9A1	Hs.154850	0.8	-	-	-	-	-	-	-	-	-
COL9A3	Hs.53563	0.47	-	-	-	-	-	-	-	-	-
CONTGF	Hs.194678	0.93	1.5	1.17	1.31	-	0.95	1.02	-	2.25	0.6
CREB1	Hs.79194	1.84	0.83	-	-	-	-	-	1.29	-	-
CREBPA	Hs.149	0.94	0.89	1.11	0.85	0.6	0.82	0.52	0.95	0.78	1.12
CREB-RP	Hs.42853	1.22	1.03	-	-	-	0.92	0.61	1.01	-	0.53
CREM	Hs.155924	1.64	0.79	-	1.27	0.52	1.1	1.44	1.39	0.81	0.57
CSF1R	Hs.174142	2.57	1.99	0.83	2.22	-	0.74	1.9	6.25	1.18	4.33
CSF2RA	Hs.182378	1.19	1.74	0.74	1.51	-	0.97	1.97	2.7	1.97	1.91
CSF3R	Hs.2175	-	1.9	-	-	-	-	-	-	-	-
CSK	Hs.77793	0.91	1.48	1.21	2.56	0.81	1.2	1.59	2.54	1.08	2.15
CTGF	Hs.75511	0.35	0.07	0.06	0.1	0.35	0.75	0.14	0.26	0.83	0.27
CX3CR1	Hs.78913	-	3.61	-	0.91	-	-	3.19	8.12	1.64	4.68
CXCR4	Hs.89414	2.56	4.53	1.21	12.11	1.11	1.43	5.34	9.4	3.52	8.65
CYPA	Hs.342389	0.7	1.05	1.36	-	-	1.79	1.25	1.93	0.88	2.22
CYR61	Hs.8867	0.56	0.1	0.22	0.33	0.25	0.81	0.72	0.74	1.1	0.58
DAF	Hs.1369	1.14	-	-	0.52	1.95	0.89	0.72	0.68	0.79	1.56
DDR1	Hs.75562	0.19	0.45	0.69	0.37	0.99	1.04	1.33	0.7	0.28	0.7
DDR3	Hs.180338	0.99	-	-	-	-	1.39	-	-	-	-
DPP4	Hs.44926	0.78	1.04	-	0.49	-	0.97	0.89	0.42	-	0.08
E4BP4	Hs.79334	2.14	1.24	1.78	1.47	-	0.77	0.88	2.73	2.66	0.54
EDG1	Hs.154210	6.3	2.55	2.12	1.73	-	0.77	2.67	4.77	-	0.92
EDG2	Hs.75794	-	-	-	-	-	-	1.76	-	-	-
ENG	Hs.76753	2.79	0.94	1.13	-	0.55	-	1.07	1.7	0.79	0.62

Gene name	UniGene	266	271	275	277	333	493	258	261	269	274
ENIGMA	Hs.102948	1.47	0.44	0.54	0.73	-	-	-	1.49	1.23	-
FAK1	Hs.740	2.56	0.95	1.37	0.67	0.67	0.66	0.71	0.88	-	-
FBLN1_1	Hs.79732	0.15	-	0.08	-	-	0.69	0.02	-	-	-
FBLN2	Hs.198862	3.98	-	-	-	-	-	-	1.27	-	-
FBXW1B	Hs.21229	1.16	-	-	0.73	2.08	0.51	0.51	0.81	-	-
FCGR1A	Hs.77424	4.66	3.27	1.14	6.74	1.91	1.19	3.88	1.35	6.02	8.77
FCGR2C_HUMAN	Hs.78864	1.83	1.82	0.51	13.68	0.95	1.31	2.97	2.51	3.59	4.78
FCGR3A_HUMAN	Hs.176663	3.57	9.19	2.77	8.46	-	0.69	6.84	6.7	26.61	15.7
FGR	Hs.1422	1.31	1.32	-	-	-	-	-	-	-	-
FIBRILLIN1	Hs.750	1.47	0.34	0.61	1.41	1.64	0.77	0.85	1.43	1.4	2.04
FIBROMODULIN	Hs.230	-	-	-	-	-	-	-	-	2.64	5.22
FIBRONECTIN	Hs.287820	3.2	1.11	2.72	3.58	1.11	0.55	1.74	3.58	6.9	5.02
FIP2	Hs.278898	0.82	1.01	1.46	1	0.29	1.12	1.16	0.72	0.91	0.85
FKHR	Hs.170133	1.06	-	-	-	-	-	-	0.86	-	-
FKHRL1	Hs.380831	1.17	1.41	1.66	1.11	-	-	0.8	0.83	1.03	0.6
FLT3	Hs.385	-	-	-	-	-	-	0.69	-	-	-
FOSL2	Hs.301612	0.23	0.23	0.1	0.08	0.21	0.96	0.05	0.42	0.12	0.19
FRE	Hs.153684	2.32	1.86	0.92	2.51	-	0.81	1.28	2.69	2.72	0.58
FREAC1	Hs.155591	0.85	1.01	-	0.49	1.27	1.17	1.08	1.44	0.73	0.94
FRIZZLED3	Hs.40735	0.73	0.86	0.97	1.02	1.21	1.71	0.99	1.56	0.74	1.53
FTH	Hs.62954	0.71	1.09	2.38	0.63	1.52	1.21	0.99	1.08	1.69	0.97
FY	Hs.183	1.99	-	0.14	-	0.66	1.83	0.62	1.69	-	0.71
FYN	Hs.169370	1.9	0.83	0.91	0.41	-	1.06	0.85	0.53	-	-
FZD4	Hs.19545	1.5	0.76	0.82	1.27	1.08	0.74	0.84	1.02	-	0.61
FZD6	Hs.114218	1.05	0.7	0.52	0.99	1.38	-	1.04	0.65	0.58	0.91
GADD153	Hs.129913	0.88	1.65	-	1.41	5.76	1.63	1.01	0.77	0.48	0.67
GADD34	Hs.76556	0.85	0.96	1.06	1.08	0.7	1.36	1.19	0.89	0.83	1.11
GADD45	Hs.80409	0.58	1.08	0.83	0.32	1.23	1.64	0.27	0.61	0.58	0.83
GAP1	Hs.119274	0.48	0.66	-	0.62	-	-	0.69	-	-	-
GAPD	Hs.169476	1.71	1.96	3.5	1.86	2.32	1.58	1.6	2.04	2.6	2.74
GAS2	Hs.129818	-	-	-	-	5.65	-	0.91	-	-	-
GAS3	Hs.103724	3.9	6.18	-	1.61	-	1.96	0.93	3.22	1.6	1.29
GDF15_2	Hs.296638	0.36	0.74	0.3	0.13	1.89	1.57	0.48	0.27	0.15	0.22
GDF3_1	Hs.86232	1.04	-	-	-	-	-	-	-	-	-
GJA1_2	Hs.74471	2.92	1.67	1.07	1.02	0.67	0.71	2	1.93	1.25	1.53
GM-CSF	Hs.1349	-	-	-	-	-	-	-	-	-	-
GNA13	Hs.1666	1.48	2.71	-	2.61	-	-	0.93	0.8	-	-
GNAI1_1	Hs.203862	1.79	1.42	-	3.84	-	-	0.83	1.19	-	0.75
GNAI3	Hs.73799	1.46	0.77	0.78	1.26	0.54	0.75	1.01	0.89	0.87	1.22
GNAQ	Hs.380144	2.61	4.52	2.54	1.13	-	0.75	1.54	2.11	1.8	0.9
GRB2	Hs.381152	0.86	0.63	1.01	0.69	0.56	0.96	0.72	0.83	1.49	0.83
GREMLIN	Hs.40098	0.35	-	-	-	-	-	-	-	-	-
GRO1_HUMAN	Hs.789	-	-	-	-	-	-	-	-	1.29	-
HCK	Hs.89555	1.84	1.98	1.04	17.58	2.15	0.85	8.22	3.1	1.7	8.58
HEVIN	Hs.75445	12.76	4.29	2.57	3.38	16.9	1.08	3.07	7.78	1.24	1.86
HLF	Hs.250692	0.64	-	-	-	-	-	-	-	-	-
HPRT	Hs.82314	-	-	-	-	-	-	-	-	0.91	3.05
HSC73	Hs.180414	0.65	0.49	0.82	0.54	0.94	0.97	0.59	0.43	0.74	0.7
HSP70.1	Hs.8997	0.68	0.86	1.29	0.35	0.6	1	0.39	0.75	0.45	0.42
HSPA1L	Hs.80288	1.52	-	-	-	-	-	-	-	-	-
HSPA9	Hs.3069	0.51	0.99	0.7	0.5	1.4	1.02	0.49	0.53	0.63	0.5
HSPG2	Hs.211573	3.03	-	2.37	-	-	0.46	1.48	3.96	-	1.29
HSR.1	Hs.44581	1.13	-	-	-	-	-	-	-	0.88	1.64
IAP1	Hs.127799	0.73	5.82	0.89	2.43	0.96	0.48	3.31	2.53	6.05	1.99
ICAM1	Hs.168383	0.7	0.86	0.72	0.45	0.43	0.85	0.61	0.73	0.68	0.91
ICAM3	Hs.99995	0.59	1.14	0.78	1.53	1.12	1.99	1.08	1.24	0.76	1
IFNGR1	Hs.180866	1.87	1.67	0.96	1.73	1.39	1.15	1.56	1.49	2.82	2.85
IKBA	Hs.81328	1.01	2.54	1.55	1.33	0.33	1.49	1.1	2.23	0.61	0.56
IKBB	Hs.9731	0.66	0.91	-	-	-	-	-	-	-	-
IKBE	Hs.182885	-	1.01	0.99	-	-	1.28	4.97	-	1.73	3.26
IKKA	Hs.198998	1.21	-	-	-	-	-	0.55	0.49	0.8	0.58
IKKB	Hs.226573	0.57	0.35	-	-	1.68	0.64	0.38	0.37	0.6	0.38
IKKG	Hs.43505	0.96	1.13	-	-	-	-	0.51	0.8	-	0.54
IL11	Hs.1721	2.06	1.1	0.6	1.11	-	0.79	1.24	3.05	2.8	0.67
IL15_1	Hs.168132	-	1.22	-	1.29	-	0.78	1.59	-	-	-
IL16	Hs.82127	0.79	1.76	0.74	5.02	-	1.6	2.25	3.05	1.62	1.75
IL18	Hs.83077	0.27	0.66	0.5	0.51	4.92	1.45	1.38	0.85	1.11	2.5
IL1B	Hs.126256	-	2.87	-	-	-	1.53	2.61	-	1.45	0.77
IL1R1	Hs.82112	0.85	0.61	-	0.66	-	-	0.43	-	-	0.81
IL1R2	Hs.25333	2.3	-	-	0.49	-	-	0.09	-	0.71	5.55
IL2RG	Hs.84	0.76	1.64	0.49	3.32	-	1.26	2.69	1.62	-	0.95
IL3RA	Hs.172689	2.77	0.69	1.11	0.61	0.75	1.23	1.29	1.75	0.49	0.59
IL4	Hs.73917	-	0.63	-	0.55	-	1.37	0.75	0.71	0.45	0.85
IL4R	Hs.75545	1.77	1.34	0.92	-	-	1	1.05	1.1	-	0.74
IL5RA	Hs.68876	-	-	-	-	-	-	-	-	0.94	3.54
IL6	Hs.93913	2.76	-	-	-	-	1.02	1.29	1.48	1.38	1.8
IL6R	Hs.193400	-	1.14	-	0.75	-	-	0.64	0.61	0.75	-
IL6ST	Hs.82065	0.89	0.93	-	0.47	0.75	0.77	0.53	0.49	-	0.43
IL7	Hs.72927	-	0.89	-	1.44	-	1.41	0.82	0.75	0.83	0.92
IL7R	Hs.362807	0.17	-	-	-	-	-	1.43	-	-	-
IL8_HUMA	Hs.624	0.7	0.72	-	-	0.64	1.31	1.18	1.54	1.31	1.32
IL8RB-IL8RA_HUMAN	Hs.194778 Hs.846	0.48	-	-	-	-	-	-	0.33	0.52	-

Gene name	UniGene	266	271	275	277	333	493	258	261	269	274
ILF	Hs.296281	0.94	-	-	-	-	-	-	-	-	-
INTEGRINA7	Hs.74369	2.92	-	-	-	-	-	-	-	-	-
INTEGRINA8	Hs.91296	0.42	-	3.68	-	-	-	-	1.09	-	-
INTEGRINB5	Hs.149846	-	-	-	-	-	-	-	-	0.64	-
INTEGRINB6	Hs.57664	0.51	0.04	0.08	-	-	-	0.63	0.88	-	0.7
INTEGRINB7	Hs.1741	0.43	2.48	0.97	1.37	1.31	1.21	1.37	1.74	0.64	0.6
INTEGRINB8	Hs.355722	-	-	-	-	-	-	-	-	-	0.98
IQGAP1	Hs.1742	1.94	1	0.81	0.89	3.05	0.4	1.14	1.3	1.36	1.61
IQGAP2	Hs.78993	0.56	0.73	-	-	2.79	-	0.2	0.22	-	-
ITGA1_1	Hs.116774	2.54	0.99	1.13	1.36	2.28	0.54	2.13	3.44	5.03	1.24
ITGA1_2	Hs.116774	1.92	0.66	1.62	1.66	1.17	0.46	1.45	1.7	2.04	1.22
ITGA3	Hs.265829	0.76	0.83	0.66	0.71	-	-	0.91	1.22	2.33	2.19
ITGA4	Hs.40034	-	1.61	-	-	-	-	1.62	-	-	-
ITGA5	Hs.149609	7.05	1.32	-	2.49	0.93	0.61	2.48	2.72	1.35	2.25
ITGA6	Hs.227730	3.29	1.04	1.52	0.87	2.56	0.65	1.23	0.84	-	0.35
ITGAE	Hs.851	0.61	-	-	-	-	1.63	0.92	0.73	0.53	0.92
ITGAV	Hs.295726	1.27	0.89	-	0.95	3.52	-	0.98	0.78	1.62	1.66
ITGB1	Hs.287797	2.41	0.71	0.85	-	0.76	0.48	1.34	1.57	2.5	1.86
ITGB2	Hs.83968	1.67	2.61	1.21	4.34	1.21	0.98	4.5	3.67	2.97	6.25
ITGB3	Hs.87149	0.54	0.12	-	-	1.09	-	0.54	0.32	-	-
ITGB4	Hs.85266	1.31	0.75	-	1.04	-	-	-	1.14	-	2.29
JUNB	Hs.198951	4.37	1.74	0.81	0.65	0.9	1.07	1.31	1.29	0.86	0.96
KAI1	Hs.323949	0.25	0.49	0.26	-	1.64	0.8	0.29	0.36	0.84	3
KIAA0170	Hs.277585	0.95	-	1.06	-	-	-	-	0.46	0.71	0.48
KIAA0538	Hs.184367	2.07	-	-	1.24	-	-	-	-	-	-
KIAA0646	Hs.24439	0.6	0.48	0.57	0.39	0.54	0.94	0.52	0.34	0.37	-
KIAA1041	Hs.26023	1.15	0.65	1.03	2.92	0.36	1.5	8.63	1.21	2.33	0.42
KIT	Hs.81665	-	-	-	-	11.97	-	-	-	-	-
KLRD1	Hs.41682	1.88	-	-	-	-	0.96	12.85	-	-	-
LAMA3	Hs.83450	0.72	1.08	0.81	-	-	-	0.73	0.89	0.9	0.5
LAMA4	Hs.78672	7.51	2.41	1.98	7.44	4.43	0.5	1.62	6.21	13.5	8.06
LAMA5	Hs.11669	0.92	0.52	1.3	1.69	0.95	1.07	1.37	1.42	-	1.48
LAMB1	Hs.82124	1.01	0.25	0.43	0.24	0.48	0.62	0.39	0.76	0.37	0.71
LAMB3	Hs.75517	-	-	-	-	-	0.71	-	-	0.82	-
LAMG1	Hs.214982	1.69	0.7	1.08	1.38	-	0.75	1.17	1.98	0.65	1.44
LAMP1	Hs.150101	0.52	0.43	-	0.34	0.79	0.93	0.35	0.43	0.9	0.34
LAMP2	Hs.8262	0.61	1.09	1.09	0.97	1.73	1.15	0.65	0.77	0.64	0.54
LAP18	Hs.250811	0.58	0.48	0.66	0.55	0.44	1.29	0.56	0.72	0.33	0.81
LCK	Hs.1765	0.49	-	-	-	-	1.57	1.33	-	-	-
LCP2	Hs.2488	3.54	3.03	0.51	-	-	0.71	-	-	3.31	0.92
LIG3	Hs.100299	0.41	0.79	0.77	-	-	-	0.38	-	-	-
LIG4	Hs.166091	0.78	-	-	-	-	-	-	-	-	-
LIM	Hs.154103	1.1	0.66	0.55	0.5	0.96	0.55	0.53	0.68	0.47	0.47
LINK	Hs.2799	-	-	-	-	-	-	11.32	6.74	11.98	-
LRP1	Hs.236894	1.23	1.69	-	-	-	-	-	0.68	-	4.32
LTBP1	Hs.241257	1.26	-	-	-	-	0.78	-	0.86	-	-
LTBP2	Hs.83337	0.66	0.79	0.85	-	0.55	1.16	0.7	0.71	0.58	0.43
LTBP4	Hs.85087	0.47	0.37	-	-	-	1.1	0.31	0.62	0.59	0.5
LUMAN	Hs.287921	0.81	1.41	1.4	1.45	1.61	1.76	1.42	0.99	0.86	1.86
LUMICAN	Hs.79914	0.29	0.04	0.03	-	-	1.16	-	-	0.66	-
LYN	Hs.80887	1.88	1.9	1.64	2.16	0.82	0.94	2.56	1.87	2.48	3.52
LYSYLOXIDASE	Hs.102267	-	0.39	-	-	-	1	-	3.07	10.03	9.65
MAFG	Hs.252229	1.04	1.1	0.93	1.12	-	1.36	0.86	0.83	-	-
MAGP1	Hs.83551	0.49	-	-	-	-	1.4	-	-	0.61	-
MAPK14	Hs.79107	1.34	0.9	-	1.22	-	-	1.01	0.83	-	0.95
MAPK3	Hs.861	2.21	0.94	0.99	0.49	-	1.27	-	0.52	-	-
MAPK7	Hs.3080	1.29	1.04	-	-	-	-	-	-	-	-
MAPK9	Hs.246857	1.33	0.93	-	0.87	0.94	0.83	0.81	1.22	0.68	0.46
MATK	Hs.274	-	-	-	-	-	-	-	-	-	5.14
MATRILIN2	Hs.19368	0.39	0.9	-	0.2	-	-	0.18	1.14	-	0.5
MATRIXGLA	Hs.365706	0.49	0.3	0.41	0.68	0.46	1.69	0.44	1.02	1.01	0.36
MCL1	Hs.86386	2	1.08	0.59	1.06	1.35	0.43	0.94	1.07	1.01	1.14
MCP	Hs.83532	1.35	1.3	0.98	0.88	1.64	0.67	0.84	0.79	0.81	0.69
MDC9	Hs.2442	1.8	0.72	-	0.88	1.68	0.53	1.96	1.55	1.93	1.8
MDU1	Hs.79748	0.63	0.93	-	0.39	2.28	1.66	0.25	0.4	0.36	0.21
MEGF5	Hs.57929	1.48	-	-	-	-	-	-	-	-	-
MFAP3	Hs.28785	0.58	0.84	1.04	0.59	0.65	1.26	0.84	0.87	0.83	0.68
MIC2	Hs.433387	0.95	0.97	1.78	1.85	0.45	1.2	1.68	2.36	3.01	0.95
MIP2B_HUMAN	Hs.89690	0.63	0.61	0.98	0.85	-	0.99	0.52	1.3	1.01	1.01
MME	Hs.1298	0.12	0.59	1.03	0.15	-	0.55	0.25	0.19	-	0.00
MMP1_HUMAN	Hs.83169	1.12	-	-	4.71	-	4.07	-	2.36	-	-
MMP11	Hs.155324	1.24	-	-	2.08	-	0.66	-	-	-	-
MMP15	Hs.80343	0.83	-	-	-	0.9	8.43	-	0.64	-	-
MMP18	Hs.154057	-	-	-	-	-	-	-	-	2.43	3.43
MMP2	Hs.111301	1.2	-	-	-	-	1.01	-	2.54	4.48	1.51
MMP7	Hs.2256	0.12	0.0087	0.0069	-	0.94	7.68	-	-	1.01	-
MMP8	Hs.73862	-	-	-	-	-	-	-	-	-	-
MMP9	Hs.151738	1.08	-	-	-	-	5.12	-	-	2.25	-
MPP1	Hs.1861	0.73	1.37	1.19	0.77	0.78	-	0.51	0.51	0.61	0.39
MS4A2	Hs.89751	0.08	-	-	-	-	-	-	-	-	-
MSP58	Hs.25313	0.64	1.05	1.2	0.86	1.48	1.52	0.65	0.84	0.56	0.63
MST1R	Hs.2942	0.69	0.82	0.65	0.31	0.8	0.84	0.63	0.47	0.56	0.5

Gene name	UniGene	266	271	275	277	333	493	258	261	269	274
MUPP1	Hs.169378	1.29	2.54	0.83	-	-	0.86	-	1.16	-	-
NBS1	Hs.25812	-	1.43	-	-	-	-	1.27	-	-	-
NCAM1_1	Hs.167988	-	-	-	-	2.36	0.74	0.88	0.32	-	-
NED4	Hs.1565	0.78	1.01	-	-	-	-	-	0.65	-	1.43
NFAT3	Hs.77810	0.82	-	-	-	-	-	-	-	-	-
NFATX	Hs.172674	1.21	1.66	1.22	0.83	0.46	0.68	0.98	1.29	0.78	0.45
NF-E2	Hs.75643	-	-	-	-	-	-	-	-	-	-
NFE2L1	Hs.83469	1.05	1.28	1.03	0.4	0.86	0.72	0.48	0.68	0.74	0.52
NFKB1	Hs.83428	1.08	1.57	1.61	1.2	0.9	1.31	1.35	1.5	0.93	1.28
NFKB2	Hs.73090	0.76	0.62	-	-	-	-	-	-	-	-
NFKB3	Hs.75569	1.63	2.38	0.88	-	1.16	1.27	0.75	1.02	-	-
NIDOGEN	Hs.348994	1.87	0.89	1.34	-	-	-	0.85	1.22	0.81	-
NRF2	Hs.155396	0.61	0.44	0.58	0.48	0.65	0.74	0.91	0.6	0.59	0.54
NT5	Hs.153952	2.23	0.98	0.86	0.41	-	-	0.34	0.34	2.07	0.41
OPN	Hs.313	0.07	0.14	0.57	0.13	5.3	1.42	0.56	0.58	2.04	0.59
OSF	Hs.95821	1.28	0.64	0.75	0.78	1.91	1.06	0.98	0.97	1.17	0.72
OSP94	Hs.71992	-	-	-	-	2.13	-	1.56	0.44	-	0.58
OSTEOCALCIN	Hs.2558	0.61	1.82	-	-	-	5.04	-	-	-	-
P5	Hs.1846	1.38	1.59	0.92	-	-	0.85	0.46	1.14	-	1.18
P73_1	Hs.247753	0.55	0.94	0.81	0.37	0.62	1.2	0.72	0.59	0.57	0.5
PAI1	Hs.82085	5.62	0.73	-	16.7	-	0.74	4.21	2.13	5.19	16.0
PAR2	Hs.154299	-	1.3	0.6	4.49	-	-	0.73	0.83	0.45	1.25
PCNA	Hs.78996	1.03	1.13	1.1	1.21	1.19	1.11	1.03	0.95	1.02	1.94
PDGA	Hs.37040	-	0.7	0.79	-	-	1.09	-	1.35	-	0.65
PDGB	Hs.1976	1.98	0.59	1.06	0.34	-	0.69	0.84	0.72	-	-
PDGFRB	Hs.76144	2.09	1.88	-	3.53	-	0.48	1.34	1.67	6.32	1.09
PDZK1	Hs.15456	0.18	0.68	1.74	0.4	0.02	2.43	0.55	0.5	0.33	0.05
PESCADILLO	Hs.13501	0.72	1.63	1.32	1.13	0.99	0.83	0.92	1.44	1.29	1.11
PGS2	Hs.433989	0.06	0.02	0.01	0.09	0.12	1.61	0.00965	0.1	0.24	0.02
PIK3C2A	Hs.249235	1.44	0.99	0.97	0.78	0.86	-	0.76	0.63	0.6	0.59
PIK3CA	Hs.85701	1.62	-	1.12	0.72	-	-	0.76	0.96	1.44	-
PIK3CB	Hs.239818	0.47	0.76	-	0.46	-	0.52	0.66	0.45	0.35	0.38
PIK3R1	Hs.6241	0.84	0.87	-	0.42	-	0.68	0.49	0.73	1.92	0.98
PIK3R3	Hs.372548	6.29	0.88	-	0.68	-	-	1.26	-	-	-
PKCD	Hs.155342	0.6	1.09	-	0.55	4.2	1.15	0.39	0.37	0.51	0.32
PLA2G4	Hs.211587	-	0.44	-	-	-	-	-	-	-	-
PLC	Hs.153322	0.31	0.13	-	0.07	0.22	-	0.07	0.06	-	0.02
PLCB1	Hs.41143	0.86	1.18	0.92	0.6	-	-	1.05	0.77	0.76	0.49
PLCG1	Hs.268177	2	0.6	-	-	-	-	0.56	0.58	-	-
PLCG2	Hs.75648	0.43	0.22	-	0.15	5.15	1.03	0.31	0.17	-	0.22
PLGF	Hs.2894	9.86	54.43	5.32	36.77	-	1.02	7.78	29.87	27.68	5.68
PNP	Hs.120330	0.64	-	-	-	-	-	-	-	0.8	0.67
PPOL	Hs.177766	0.84	1.05	1.19	0.81	0.49	0.98	0.88	0.72	0.98	0.86
PRELP	Hs.76494	0.81	-	-	-	-	-	-	-	-	3.61
PRK2	Hs.69171	1.19	0.6	1.89	0.45	-	0.67	0.86	0.77	1.48	0.57
PRKCB_1	Hs.77202	-	1.57	-	-	-	0.63	1.43	-	0.44	-
PRKCB_2	Hs.77202	0.76	-	-	-	0.35	0.82	0.63	-	0.66	0.23
PRKCH	Hs.315366	4.97	1.31	1.49	4.32	-	1.02	3.09	2.1	2.12	1.16
PRSS11	Hs.75111	1.64	0.55	-	0.35	0.41	0.83	0.52	0.79	2.37	0.66
PTAFR	Hs.46	0.9	1.76	-	-	-	1.04	-	2	2.34	-
PTGD	Hs.158326	0.67	-	1.28	-	-	0.84	-	0.99	0.56	0.55
PTGFR	Hs.89418	0.7	-	-	-	-	-	-	-	-	-
PTP	Hs.211595	0.27	0.53	-	0.26	0.18	-	0.33	0.24	-	0.27
PTP1C	Hs.63489	0.86	1.48	1.1	1	-	1.23	1.38	1.21	0.81	1.72
PTPN12	Hs.62	2.58	1.48	1.4	2.11	-	0.7	1.65	2.32	1.68	2.07
PTPN3	Hs.153932	0.29	0.63	-	0.64	1.98	-	0.51	0.27	-	-
PTPN4	Hs.73826	0.9	0.36	1.02	0.45	0.57	1.02	0.76	0.34	0.32	0.38
PVS_HUMAN	Hs.171844	-	-	-	-	-	0.98	-	-	-	-
RAI: (RAI)	Hs.324051	2.25	1.16	1.77	2.19	-	1.65	2.17	3.26	1.07	2.97
RAR	Hs.302498	0.55	0.63	-	0.31	1.12	1.69	0.39	0.35	-	0.26
RASA1_2	Hs.758	0.61	0.85	0.4	0.35	0.5	-	0.52	0.3	0.25	0.33
RELB	Hs.858	0.98	0.87	1.15	-	-	-	-	3.67	-	1.34
RPS7	Hs.301547	0.68	0.75	1.16	1.67	0.72	1.73	1.38	1.21	0.77	1.04
RRAS	Hs.9651	0.86	2.26	1.14	1.5	0.7	2.05	1.42	1.49	1.14	2.76
RYUDOCAN	Hs.252189	-	0.5	-	-	2.93	-	-	0.36	-	0.86
SARP2	Hs.7306	0.5	0.28	0.49	0.24	0.28	1.34	0.62	0.54	0.93	0.61
SELE	Hs.89546	1.14	0.66	0.75	-	3.21	1.42	1.11	0.79	0.52	0.83
SELL	Hs.82848	0.72	1.72	-	-	-	0.9	2.3	-	0.99	-
SELPLG	Hs.79283	0.8	1.86	0.85	0.94	-	1.36	1.56	1.03	1.07	3.94
SERPINA1_1_HUMAN	Hs.297681	1.07	3.25	2.59	1.56	0.27	0.97	1.12	4.02	2.61	2
SIP1_1	Hs.101813	2.05	1.1	-	-	0.49	0.85	0.54	-	-	-
SIP1_2	-	2.1	-	-	-	-	-	-	-	-	-
SIPA1	Hs.7019	1.1	0.87	1.01	0.53	1.03	0.89	1.04	0.82	0.86	0.75
SMPD2	Hs.55235	0.47	0.66	0.95	0.72	-	-	0.77	-	0.58	0.96
SOCS1	Hs.50640	0.55	0.78	1.07	0.84	1.43	1.61	1.14	1.33	0.78	1.66
SOCS2	Hs.110776	2.19	-	-	-	-	-	0.68	0.84	-	-
SOCS3	Hs.345728	3.57	-	-	-	-	0.68	-	-	-	-
SOD1	Hs.75428	0.56	0.75	0.91	0.59	0.67	1.83	0.6	0.62	0.4	0.42
SOS1	Hs.326392	1.02	0.56	0.99	0.56	-	0.95	0.39	0.56	0.69	0.42
SPARC	Hs.111779	4.5	1.15	2.33	1.63	3.11	0.65	3.05	2.54	6.92	2.73
SPOCK	Hs.93029	-	-	-	-	-	-	-	-	6.41	1.11
SRC	Hs.198298	0.46	0.94	0.72	0.99	0.44	1.43	1.05	0.49	0.33	0.7

Gene name	UniGene	266	271	275	277	333	493	258	261	269	274
SSB2	Hs.334697	-	-	-	-	-	-	-	-	-	0.56
STAT1	Hs.21486	1.28	1.06	1.23	2.35	0.49	-	1.96	1.24	1.07	1.49
STAT2	Hs.72988	2.81	1.43	1.34	-	-	1.42	7.83	1.44	1.27	0.96
STAT3	Hs.321677	1.03	1.01	0.72	1.05	0.34	0.69	0.99	0.98	0.89	1.1
STAT5A	Hs.167503	0.73	0.8	0.68	1.13	0.23	1.39	0.58	0.75	0.87	1.16
STAT5B	Hs.244613	1.58	1.08	1.39	1.32	-	0.64	1.1	0.86	1.09	1.07
STAT6	Hs.181015	1.15	1.36	1.52	0.82	-	-	-	1.43	-	-
SYCL	Hs.8180	1.81	0.73	0.84	1.66	1.33	1.02	1.2	1.21	1.42	1.77
SYK	Hs.74101	0.83	-	-	-	-	-	-	-	-	-
SYNDECAN1	Hs.82109	-	0.4	-	0.4	-	0.79	0.17	0.47	0.89	0.35
SYNDECAN2	Hs.1501	0.99	1.16	1.6	1.25	4.65	0.66	1.05	1.01	0.66	0.61
SYNDECAN3	Hs.158287	0.61	0.62	0.89	-	-	0.88	0.79	0.61	0.53	0.5
SYNGAP2	Hs.221922	0.66	-	-	-	-	-	-	-	-	-
TAX1	Hs.12956	0.82	0.55	0.89	0.83	0.68	1.5	0.71	1.09	1.93	2.31
TAX2	Hs.6454	-	-	-	-	-	-	-	-	-	-
TAX33	Hs.178215	-	2.18	2.44	1.25	3.67	2.76	1.29	0.45	-	-
TAX40	Hs.112933	-	0.96	-	-	-	1.97	-	-	-	-
TCF12	Hs.21704	1.54	1.32	-	0.69	-	-	0.72	0.76	0.83	0.89
TCF4	Hs.326198	2.2	1	1.5	1.71	0.62	0.91	2.18	2.31	1.15	1.16
TENASCINC	Hs.289114	0.66	0.19	-	-	-	0.85	-	0.91	0.74	-
TFRC	Hs.77356	1.25	1.41	-	0.51	2.15	-	0.76	0.54	-	0.73
TGF1	Hs.1103	1.48	1.28	1.59	1.85	1.03	0.96	2.28	2.85	2.86	1.44
TGF3	Hs.2025	-	-	0.7	0.54	-	0.73	0.82	0.73	0.67	1.63
TGFA55	Hs.170009	0.58	1.45	1.13	0.84	-	-	1.16	0.6	0.82	0.66
THBD	Hs.2030	2.23	-	0.5	-	-	0.45	0.76	-	-	1.33
THROMBOSPONDIN1	Hs.87409	0.65	0.42	0.4	0.65	-	0.63	0.54	1.69	3.01	1.79
THROMBOSPONDIN2	Hs.108623	0.65	0.09	-	5.4	-	0.55	0.6	0.65	3.61	4.96
THROMBOSPONDIN5	Hs.1584	0.62	-	-	-	-	-	-	-	-	-
THY1	Hs.125359	4.22	0.33	2.07	0.3	0.08	0.71	0.36	0.26	1.13	0.3
TIMP1	Hs.5831	1.76	0.69	0.52	6.31	0.86	1.19	4.35	3.97	5.97	5.75
TIMP2	Hs.6441	0.73	0.83	0.97	1.06	-	1.17	0.85	1.08	0.88	1.63
TIMP3	Hs.245188	1.1	2.51	1.22	0.46	2.21	0.97	1.03	1.07	-	0.2
TKT	Hs.71891	1.02	-	-	-	-	-	-	-	-	-
TNFC	Hs.890	0.21	0.45	-	3.02	-	1.98	1.59	0.94	0.33	0.96
TNFR1	Hs.159	2.24	1.33	1.69	4	-	-	1.5	1.42	1.69	0.77
TNFRSF11A	Hs.114676	-	-	-	-	-	-	0.32	-	-	-
TNFRSF1B	Hs.256278	2.06	0.9	-	-	-	0.81	1.54	1.5	-	1.42
TNFRSF5	Hs.25648	2.21	4.23	1.97	2.29	1.34	1.49	3.8	1.7	1.71	3.34
TNFRSF6	Hs.82359	-	1.47	0.67	-	-	0.8	2.43	0.54	-	-
TNFRSF7	Hs.180841	-	2	-	-	-	1.92	-	-	-	-
TNFSF12	Hs.26401	1.37	2.06	1.02	1.15	-	1.53	0.94	1.18	0.52	0.42
TNFSF7	Hs.99899	-	26.71	13.35	14.51	-	4.16	39	80.4	35.73	43.0
TNFSF9	Hs.1524	-	-	-	-	-	-	-	45.53	-	2.64
TP53BP1	Hs.170263	0.66	1.65	0.81	-	-	0.86	0.8	1.15	0.74	-
TPA	Hs.274404	0.5	0.28	0.48	0.08	0.06	0.91	0.19	0.28	0.07	0.09
TRAIL	Hs.83429	1.27	0.71	1.13	1.3	0.22	1.92	1.31	1.33	3.3	2.56
TRAILR1_HUMAN	Hs.249190	0.99	1.18	1.18	2.27	-	1.4	1.62	1.27	-	1.09
TRAILR2	Hs.51233	1.86	1.86	1.29	3.33	2.92	0.63	2.56	2.25	1.53	1.76
TRAILR3_HUMAN	Hs.119684	1.89	-	-	-	-	1.22	0.61	0.97	-	2.6
TRAILR4_HUMAN	Hs.129844	-	-	-	-	-	-	0.7	2.35	-	0.52
TRAIN	Hs.283615	-	0.98	-	-	-	-	-	-	-	-
TUBA_HUMAN	Hs.278242	1.26	1.68	1.34	1.9	2.04	1.12	2.54	2.07	1.39	4.03
TUBB1-TUBB5_HUMAN	Hs.356729 Hs.179661	1.92	1.09	1.39	2.12	0.81	0.75	1.62	2.5	1.49	2.41
UPA	Hs.77274	0.86	-	0.9	0.77	-	-	0.65	1.18	-	-
UVRAG	Hs.13137	-	-	-	-	-	-	0.77	-	-	-
VAV2	Hs.352272	-	-	-	0.26	-	-	-	-	-	-
VCAM1	Hs.109225	0.83	2.92	1.06	1.53	-	1.89	3.07	3.14	3.95	7.91
VEGC	Hs.79141	2.67	0.78	0.71	-	1.21	0.82	0.67	0.85	0.62	-
VEGF_1	Hs.73793	14.67	9.11	29.07	7.44	1.21	0.88	9.43	7.18	16.38	3.02
VEGFD	Hs.11392	0.11	-	-	-	-	-	-	-	-	-
VERSICAN	Hs.81800	0.92	-	-	-	-	0.66	-	14.92	7.03	-
VWF	Hs.110802	10.88	4.33	1.57	8.11	3.81	0.48	13.22	4.77	-	-
WSB-1	Hs.187991	0.85	0.92	1.01	0.43	0.31	0.92	1.44	0.91	1.7	1.9
WWP2	Hs.166119	0.82	0.79	0.7	0.4	0.88	0.59	0.48	0.56	-	0.43
XBP1	Hs.149923	0.91	2.14	0.78	2.1	1.76	1.06	1.87	1.16	0.5	1.18
XRCC	Hs.98493	0.96	0.9	1.34	1.31	0.66	1.42	0.83	1.17	0.55	0.56
ZO1	Hs.74614	1.67	0.51	1.11	0.45	0.91	0.88	0.69	0.74	-	0.35

B. Papillary Renal Cell Carcinoma

Ratio list of all genes present on the microarray:

Gen Name	UniGene	2828	3204	3230	2060	2810	3026
AATK: (AATK OR AATYK	Hs.514575	1.78	-	-	0.91	-	0.84
ABCP2:(ABCB2 OR TA	Hs.352018	1.75	0.88	-	0.84	1.54	-
ABCP3: (ABCB3 OR TAP	Hs.502	1.22	0.58	-	0.88	1.24	-
ABF1: (ABF-1) ACTIVA	Hs.42474	1.12	0.86	-	1.28	1.34	1.77
ABIN-2: (ABIN-2) A2	Hs.325630	0.87	1.93	-	0.52	1.40	1.21
ABIN-3: (ABIN-3) A2	Hs.208206	0.88	-	-	-	0.93	1.12

Gen Name	UniGene	2828	3204	3230	2060	2810	3026
ABR: (ABR) ACTIVE BR	Hs.434004	0.94	-	-	1.65	1.29	1.38
AC15: (RFC1 OR RFC14	Hs.166563	1.24	1.10	-	0.79	0.67	1.13
ACTA2: (ACTA2 OR ACT	Hs.208641	0.89	0.79	2.86	1.57	0.26	0.66
ACTB: (ACTB) BETA1	Hs.426930	2.24	0.77	1.38	1.16	2.18	1.82
ACVR1: (ACVR1 OR ACV	Hs.150402	0.84	1.66	-	0.96	-	0.94
ACVR2: (ACVR2) ACTIV	Hs.389846	0.84	-	-	1.19	-	1.10
ACVRL1: (ACVRL1 OR A	Hs.410104	0.92	-	-	0.96	0.57	0.79
ADAM8: (ADAM8 OR MS2	Hs.86947	1.33	0.90	-	1.12	1.47	0.94
ADCY8: (ADCY8) ADENY	Hs.120330	0.78	-	-	1.51	1.26	0.92
AF6: (MLLT4 OR AF6)	Hs.511773	0.92	-	-	1.35	0.85	0.94
AFX1: (AFX1 OR AFX O	Hs.512585	1.28	0.95	-	0.90	1.24	0.96
AGGRECAN1: (AGC1 OR	Hs.2159	0.90	-	-	0.50	-	1.98
AGRIN: (AGRN) AGRIN	Hs.273330	0.90	0.88	-	1.23	0.93	1.35
AGTRL1: (AGTRL1 OR A	Hs.438311	0.79	-	-	1.24	-	1.18
AID: (AID) ACTIVATIO	Hs.149342	0.87	-	-	-	1.36	0.78
AIF1: (AIF1 OR IBA1)	Hs.76364	1.24	-	-	1.78	1.43	1.25
AIM2: (AIM2) INTERFE	Hs.105115	1.23	-	-	1.65	1.22	0.80
AIOLOS: (ZNFN1A3) ZI	Hs.258579	1.25	-	-	1.24	1.31	0.99
AKT: (AKT1 OR RAC OR	Hs.368861	1.44	0.68	-	0.32	1.17	0.55
ALCAM: (ALCAM) CD166	Hs.10247	1.46	-	-	1.70	1.00	1.35
ALG2: (PDCD6 OR ALG2	Hs.24087	0.57	0.95	-	0.56	1.13	1.23
ALOX12-PS2: (ALOX12-	Hs.378695	-	-	-	-	-	1.91
ALOXE3: (ALOXE3) EPI	Hs.232770	0.99	-	-	2.49	0.86	1.37
ALR: (ALR) ALR.	Hs.387381	0.89	-	-	-	-	0.92
AMBP: (AMBP OR ITIL	Hs.76177	0.73	0.99	-	0.22	1.63	0.73
AMP: (MFAP1) MICROFI	Hs.61418	0.83	0.59	-	0.48	0.79	1.00
AMSH: (STAMBP OR AMS	Hs.12479	0.78	-	-	0.58	0.79	0.92
ANPEP: (ANPEP OR PEP	Hs.1239	0.66	0.87	-	0.48	0.69	0.13
AOC3: (AOC3 OR VAP1)	Hs.198241	0.60	-	-	-	-	0.79
AP1G2: (AP1G2) ADAPT	Hs.343244	0.84	-	-	0.99	0.79	1.19
APAF1: (APAF1) APOPT	-	-	-	-	-	0.85	-
APRIL: (TNFSF13 OR A	Hs.54673	0.99	0.63	-	1.43	1.34	1.34
ARHGAP1: (ARHGAP1 OR	Hs.138860	1.23	0.96	0.62	1.68	1.24	0.92
ASB-1: (KIAA1146) KI	Hs.512609	0.95	-	-	0.73	0.96	0.79
ASB-2: (ASB2) ANKYRI	Hs.182416	1.17	0.70	-	0.47	0.85	0.82
ASB-3: (ASB3) ANKYRI	Hs.40763	0.58	-	-	0.59	0.98	0.75
ASB-4: (WUGSC:H_GS3	Hs.413226	1.00	-	-	0.66	1.17	-
ATF1: (ATF1) CYCLIC-	Hs.36908	0.98	1.60	-	1.32	1.22	1.00
ATF2: (ATF2 OR CREB2	Hs.80285	0.92	0.90	-	-	0.90	0.85
ATF3: (ATF3) CYCLIC-	Hs.460	0.58	0.77	-	-	0.74	0.63
ATF4: (ATF4) CYCLIC-	Hs.181243	0.74	0.44	0.93	0.57	0.63	0.67
ATF5: (ATF5 OR ATFX)	Hs.9754	1.15	0.80	-	1.00	0.86	0.77
ATF6: (ATF6) CYCLIC-	Hs.433046	0.87	1.86	-	0.52	0.72	0.95
ATFA: (ATF7 OR ATFA)	Hs.405395	0.84	0.62	-	-	1.20	0.77
B2M: (B2M) BETA-2-MI	Hs.48516	0.62	0.70	0.75	2.55	0.69	2.72
B7-H1: B7-H1 (PD-1-L	Hs.443271	1.24	0.93	-	1.16	1.33	0.96
B7-H3: TRANSMEMBRANE	Hs.77873	-	-	-	-	0.86	0.89
BACH1: (BACH1) TRANS	Hs.154276	0.89	0.44	-	0.44	0.93	0.87
BAD: (BAD OR BBC6 OR	Hs.76366	1.50	1.47	-	0.45	1.76	0.77
BAFF: (TNFSF13B OR T	Hs.270737	1.19	0.84	-	3.78	1.29	1.27
BAG-1: (BAG1) BAG-FA	Hs.377484	0.41	0.63	-	0.17	1.42	0.68
BAG-3: (BAG3 OR BIS)	Hs.15259	1.76	-	-	0.44	0.82	0.57
BAK1-BAK2: (BAK1 OR	Hs.93213	-	-	-	-	-	0.86
BAMACAN: (BAM OR SMC	Hs.24485	0.85	-	-	0.37	0.68	0.90
BARD1: (BARD1) BRCA1	Hs.54089	1.16	-	-	1.78	1.48	1.23
BAX: (BAX) APOPTOSIS	Hs.159428	1.26	1.38	-	0.73	1.14	-
BAXBETA_HUMAN: (BAX)	Hs.159428	0.82	-	-	1.25	0.87	-
BCL1: (BCL-1 OR BC	Hs.193516	0.99	0.99	-	1.79	-	1.37
BCL2: (BCL2 OR BCL-2	Hs.79241 Hs.501181	1.34	1.39	0.78	1.27	1.52	1.65
BCL2A1: (BCL2A1 OR B	Hs.227817	-	0.56	-	-	1.00	1.16
BCL2L1: (BCL2L1 OR B	Hs.305890	-	-	-	0.85	-	0.92
BCL2L2: (BCL2L2 OR B	-	1.44	0.93	0.72	1.14	1.47	0.99
BCL2NEW_1: (BCL2L13	Hs.84063	1.31	1.23	0.66	0.89	1.43	1.68
BCL2NEW_2: (BCL2L13	Hs.410026	1.32	0.92	0.65	1.17	1.33	0.96
BCL3: (BCL3) B-CELL	Hs.310922	1.25	0.84	-	0.76	1.26	0.84
BCL6: (BCL6 OR ZNF51	Hs.310922	1.15	-	-	1.55	1.16	0.94
BCL-XL: (BCL2L1 OR B	Hs.31210	-	-	-	0.92	-	1.79
BCL-XS-XL: (BCL2L1 O	Hs.155024	0.98	-	-	0.56	0.94	0.74
BETA-TRCP: (FBW1A OR	Hs.69771	1.17	0.93	-	1.17	1.40	0.93
BF: (BF) COMPLEMENT	Hs.748	1.20	0.88	0.68	0.97	1.18	0.96
BFGFR_1_HUMAN: (FGFR	Hs.300825	0.94	-	0.43	-	0.97	0.85
BID: (BID) BH3 INTER	Hs.821	1.00	-	-	1.52	1.12	0.97
BIGLYCAN: (BGN) BONE	Hs.155419	-	-	-	2.15	-	1.15
BIK: (BIK OR BIKLK O	Hs.310769	0.83	1.24	-	-	0.77	0.82
BIP: (HSPA5 OR GRP78	Hs.289107	1.36	0.76	0.62	0.26	1.46	1.23
BM3B: (GDF1 OR BMP3	Hs.389900	-	-	-	1.16	-	1.58
BM45: (39341K13RI	Hs.8750 Hs.512788	0.90	0.46	-	0.28	0.91	0.81
BMP1: (BMP1 OR PCP-3	Hs.2171	1.52	-	-	1.82	2.25	-
BMP1: (BMP1) BONE	Hs.1274	1.15	-	-	1.33	1.34	0.97
BMP15: (BMP15 OR GDF	Hs.158317	1.10	-	-	-	-	1.19
BMP2: (BMP2 OR BMP2A	Hs.247820	0.93	1.16	-	0.89	1.45	1.12
BMP3: (BMP3 OR BMP-3	Hs.73853	-	0.45	-	-	-	1.27

Gen Name	UniGene	2828	3204	3230	2060	2810	3026
BMP4: (BMP4 OR BMP2B	Hs.121507	0.77	-	-	0.68	1.36	0.93
BMP5: (BMP5) BONE MO	Hs.68879	0.93	-	-	1.86	0.97	1.58
BMP6: (BMP6 OR BMP-6	Hs.1104	0.66	0.68	-	1.31	-	1.99
BMP7: (BMP7 OR BMP-7	Hs.285671	-	1.77	-	-	-	0.72
BMP8A-BMP8B_HUMAN: (	Hs.170195	1.13	-	-	1.23	1.29	0.99
BMPR1A: (BMPR1A OR A	Hs.409964 Hs.494158	0.68	0.99	-	0.85	1.13	0.96
BMPR1B: (BMPR1B) BON	Hs.2534	1.35	-	-	-	0.76	0.98
BNIP3: (BNIP3 OR NIP	Hs.87223	0.72	-	-	0.37	1.27	0.86
BNIP3L: (BNIP3L OR B	Hs.79428	0.63	-	-	0.52	0.93	1.12
BPGF1-Q6: (BPGF-1 OR	Hs.132955	1.39	1.18	-	1.16	1.16	1.15
BRCA1: (BRCA1) BREAS	Hs.77266	1.48	0.78	-	1.95	-	1.38
BRCA2: (BRCA2) BREAS	Hs.194143	-	0.29	-	-	-	-
BSG: (BSG) BASIGIN P	Hs.34012	1.26	0.68	-	0.25	1.17	0.38
BST1: (BST1 OR BP3 O	Hs.501293	1.67	1.00	-	0.78	1.46	0.87
BTG1: (BTG1) BTG1 PR	Hs.169998	0.24	-	-	0.75	0.82	0.71
BTG2: (BTG2 OR PC3)	Hs.255935	0.82	0.63	-	0.46	0.73	0.82
BTG3: (BTG3 OR TOB5	Hs.75462	0.33	1.33	-	0.47	1.15	0.89
BTK: (BTK OR ATK OR	Hs.77311	1.33	-	-	1.17	-	1.98
BY55: (BY55) NATURAL	Hs.159494	-	-	-	-	1.14	0.98
C1QA: (C1QA) COMPLEM	Hs.81743	2.65	1.22	-	7.64	1.41	0.83
C1S: (C1S) COMPLEMEN	Hs.9641	0.92	1.15	2.35	0.89	0.41	0.87
C2: (C2) COMPLEMENT	Hs.458355	1.34	0.92	-	1.22	1.44	0.82
C3: (C3) COMPLEMENT	Hs.2253	1.38	0.81	0.68	0.90	1.25	0.85
C3AR1: (C3AR1 OR C3R	Hs.284394	1.20	-	-	6.49	1.17	1.13
C3F: (C3F) C3F. IDEN	Hs.155935	1.76	1.43	-	0.53	1.26	0.67
C4: (C4A AND C4B) CO	Hs.300423	1.36	0.46	-	-	0.63	0.48
C4BPA: (C4BPA OR C4B	Hs.150833	1.89	-	-	-	0.99	0.85
C5R1_1: (C5R1 OR C5A	Hs.1012	0.99	1.65	0.66	2.30	1.16	1.42
C8G: (C8G) COMPLEMEN	Hs.2161	0.95	0.52	0.56	0.31	0.89	0.69
CALB1: (CALB1 OR CAB	Hs.1285	0.22	0.70	0.16	-	0.52	0.17
CALB2: (CALB2 OR CAB	Hs.65425	1.14	1.22	-	1.39	1.31	0.87
CALM2: (CALM2 OR CAM	Hs.106857	0.48	0.44	-	0.49	0.82	2.66
CANPX: (CAPN6 OR DJ9	Hs.425808	-	-	-	-	-	-
CAPN1: (CAPN1 OR CAN	Hs.169172	1.27	-	-	0.85	0.62	0.86
CAPN2: (CAPN2 OR CAN	Hs.356181	0.52	1.32	0.51	0.37	1.43	1.46
CARD4: (NOD1) CARD4/	Hs.350899	1.00	0.63	-	0.46	0.99	0.92
CASP1: (CASP1 OR IL1	Hs.19405	1.13	0.78	0.90	2.21	1.27	-
CASP1_HUMAN: (CASP1	Hs.2490	-	-	-	-	-	1.32
CASP14: (CASP14) CAS	Hs.5353	-	-	-	-	0.98	1.16
CASP2: (CASP2 OR ICH	Hs.248226	1.36	1.14	0.67	1.12	1.52	0.97
CASP3: (CASP3 OR CPP	Hs.433103	1.15	-	-	2.14	0.85	1.67
CASP4_HUMAN: (CASP4	Hs.141125	1.36	0.93	-	2.90	1.16	2.21
CASP6: (CASP6 OR MCH	Hs.74122	1.82	0.89	0.72	0.68	1.37	0.84
CASP7: (CASP7 OR MCH	Hs.3280	0.83	0.82	-	0.88	0.87	0.85
CASP8: (MCH5 OR CASP	Hs.9216	1.41	1.65	0.79	1.11	1.46	-
CASP9: (CASP9 OR MCH	Hs.243491	1.53	-	-	0.90	0.94	0.92
CBL: (CBL OR CBL2) S	Hs.329502	-	0.94	-	-	-	1.20
CBL-AP: (CAP OR SH3P	Hs.41324	1.13	-	-	0.97	0.94	0.87
CBLB: (CBLB) SIGNAL	Hs.108924	0.94	-	-	1.78	-	1.24
CBP: (PSCDBP OR CBP)	Hs.436986	0.69	0.62	-	3.79	-	1.17
CCL1_HUMAN: (SCYA1)	Hs.270	0.96	0.67	-	0.70	1.14	0.82
CCL11: (SCYA11) EOTA	Hs.72918	1.18	0.92	0.77	0.92	1.58	0.83
CCL13_HUMAN: (CCL13	Hs.54460	0.23	0.43	0.95	0.19	1.23	0.40
CCL15-CCL14_HUMAN: (	Hs.414629	0.29	0.86	0.82	0.49	0.66	-
CCL16_HUMAN: (CCL16	Hs.20144 Hs.272493	1.14	0.76	-	0.69	1.15	0.90
CCL17: (SCYA17 OR TA	Hs.10458	1.85	0.84	0.61	1.15	1.78	0.91
CCL18_HUMAN: (CCL18	Hs.66742	2.83	0.63	2.58	11.35	1.13	2.33
CCL19: (SCYA19 OR MI	Hs.16530	0.27	1.40	0.78	1.26	0.93	1.52
CCL2: (SCYA2 OR MI	Hs.50002	0.92	-	-	0.62	0.92	0.97
CCL2_HUMAN: (SCYA2 O	Hs.303649	1.88	0.49	1.20	1.35	0.67	1.99
CCL21: (SCYA21 OR SC	Hs.75498	0.43	-	-	0.90	0.99	1.24
CCL22: (SCYA22 OR MD	Hs.57907	0.95	0.74	-	0.69	1.34	1.23
CCL23_HUMAN: (CCL23	Hs.97203	0.65	1.67	-	2.87	0.99	1.43
CCL24: (CCL24 OR SCY	Hs.169191	1.17	0.99	0.59	1.32	1.32	0.99
CCL26_HUMAN: (CCL26	Hs.247838	0.71	-	-	1.23	1.14	1.44
CCL27: (SCYA27 OR IL	Hs.131342	0.83	-	-	-	1.80	1.15
CCL3-CCL3L1: (CCL3 O	Hs.225948	0.63	0.44	0.67	0.90	0.73	-
CCL3L1-CCL3: (CCL3L1	Hs.512683 Hs.73817	0.78	1.00	0.72	1.55	1.22	-
CCL4: (SCYA4 OR MIP1	Hs.512683 Hs.73817	0.76	0.63	0.84	1.87	1.20	0.89
CCL5: (SCYA5) SMALL	Hs.75703	0.83	0.64	-	2.23	1.33	0.72
CCL7: (SCYA7 OR MCP3	Hs.489044 Hs.241392	1.43	0.47	0.69	0.54	1.18	0.73
CCL8_HUMAN: (SCYA8 O	Hs.251526	0.89	-	-	-	1.11	0.84
CCNB2: (CCNB2) CYCLI	Hs.271387	2.43	-	-	1.72	1.18	1.16
CCNC: (CCNC) CYCLIN	Hs.194698	0.62	1.69	-	0.65	0.88	-
CCND1: (CCND1 OR PRA	Hs.435450	-	-	-	-	-	0.92
CCND3: (CCND3) CYCLI	Hs.371468	0.93	-	-	0.44	0.59	0.74
CCNE1: (CCNE1 OR CCN	Hs.83173	1.15	1.18	-	1.39	1.51	1.15
CCNF_2: (CCNF) G2/MI	Hs.244723	1.33	1.37	-	1.31	1.42	1.82
CCNG2: (CCNG2) CYCLI	Hs.1973	0.66	1.26	-	0.52	0.51	0.83
CCNH: (CCNH) CYCLIN	Hs.13291	1.45	-	-	0.38	1.14	1.13
CCR1: (CCR1 OR CMKBR	Hs.514	-	-	-	-	-	0.92
CCR1: (CCR1 OR GPR	Hs.301921	1.27	-	-	1.31	1.31	1.80

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CCR2-CCR5_BAD: (CCR2	Hs.278446	1.34	0.93	-	1.40	1.42	0.99
CCR3: (CCR3 OR CMKBR	-	1.22	-	-	-	-	1.24
CCR4: (CCR4 OR CMKBR	Hs.506190	-	-	-	-	0.94	1.21
CCR5-CCR2: (CCR5 OR	Hs.184926	0.69	-	-	-	0.78	1.16
CCR6: (CCR6 OR CMKBR	Hs.54443 Hs.395	0.65	0.50	-	1.27	0.79	1.17
CCR7: (CKR7 OR CMKBR	Hs.46468	1.55	-	-	1.79	0.97	1.33
CCR8: (CCR8 OR CMKBR	Hs.1652	-	0.93	-	-	-	1.62
CCR9: (CCR9 OR CMKBR	Hs.113222	0.99	-	-	1.54	1.12	1.66
CD14: (CD14) MONOCYT	Hs.225946	3.58	1.12	-	7.70	1.17	0.79
CD151: (CD151) PLATE	Hs.75627	1.16	0.72	-	0.25	0.95	0.51
CD16_HUMAN: (FCGR3A	Hs.512857	1.96	0.17	-	17.34	1.48	1.32
CD164: (CD164 OR MMG	Hs.372679	0.44	0.32	-	0.19	0.85	0.59
CD19: (CD19) B-LYMPH	Hs.43910	1.27	0.96	-	1.34	1.40	0.97
CD1A_HUMAN: (CD1A) T	Hs.96023	1.45	1.40	-	1.22	1.41	0.99
CD1B_HUMAN: (CD1B) T	Hs.1309	1.23	-	-	1.25	1.20	0.99
CD1C_HUMAN: (CD1C) T	Hs.1310	1.40	-	-	0.95	0.82	0.87
CD1D_HUMAN: (CD1D) T	Hs.1311	1.25	-	-	2.16	0.99	1.22
CD1E_HUMAN: (CD1E) T	Hs.1799	1.28	0.95	0.65	0.97	1.39	0.81
CD2: (CD2) T-CELL SU	Hs.249217	0.57	-	-	11.12	0.76	1.43
CD22: (CD22) B-CELL	Hs.89476	1.33	0.97	-	1.39	1.44	0.99
CD24: (CD24 OR CD24A	Hs.278694	0.53	-	-	1.13	0.69	4.92
CD28: (CD28) T-CELL-	Hs.262150	1.47	1.00	-	1.49	1.45	1.96
CD29_HUMAN: (CD29)	Hs.375108	1.32	-	-	1.68	0.93	1.12
CD33: (CD33) MYELOID	Hs.1987	1.13	0.44	-	1.84	0.85	2.00
CD34: (CD34) HEMATOP	Hs.83731	1.17	1.85	-	0.73	1.29	0.94
CD36: (CD36 OR GP4 O	Hs.374990	1.27	0.71	-	1.49	1.28	0.92
CD36L2: (SCARB2 OR C	Hs.443120	0.87	-	-	1.33	1.15	1.00
CD37: (CD37) LEUKOCY	Hs.349656	1.63	1.64	-	5.36	1.20	1.44
CD38: (CD38) ADP-RIB	Hs.153053	0.93	1.37	-	3.58	-	1.17
CD39: (ENTPD1 OR CD3	Hs.174944	0.88	0.65	-	2.73	0.94	1.49
CD3D: (CD3D OR T3D)	Hs.444105	0.38	-	-	6.30	0.76	1.25
CD3E: (CD3E OR T3E)	Hs.95327	0.98	1.59	-	1.85	1.35	1.48
CD3Z-CD3H: (CD3Z OR	Hs.3003	0.74	-	-	-	-	1.44
CD4: (CD4) T-CELL SU	Hs.97087	0.86	0.72	0.46	1.64	1.55	1.41
CD44_EX11-13_HUMAN:	Hs.17483	-	-	-	-	-	0.98
CD44_EX13-15_HUMAN:	Hs.306278	1.00	-	-	-	0.87	0.95
CD44_EX16-2_HUMAN:	Hs.306278	2.93	1.15	-	4.20	0.96	1.26
CD44_EX3-5_HUMAN: (C	Hs.306278	1.68	1.54	-	3.44	1.25	1.11
CD44_EX7-9_HUMAN: (C	Hs.306278	0.97	0.91	-	1.83	0.96	0.94
CD44_EX9-11_HUMAN: (	Hs.306278	1.19	-	-	1.82	1.12	1.27
CD45_EX1-11: (PTPRC	Hs.306278	0.86	1.24	-	1.39	-	-
CD45_EX29-31: (PTPRC	Hs.444324	0.78	-	-	9.85	-	0.90
CD47: (CD47 OR IAP)	Hs.444324	0.61	0.69	0.41	0.92	0.78	1.67
CD48: (CD48 OR BCM1	Hs.446414	0.46	1.16	-	1.87	0.55	2.53
CD5: (CD5 OR LEU1) T	Hs.901	0.76	-	-	-	0.71	1.27
CD52: (CDW52 OR CD52	Hs.58685	0.26	-	-	14.69	0.59	2.11
CD53: (CD53 OR MOX44	Hs.276770	0.84	-	-	8.26	1.44	1.94
CD58_HUMAN: (CD58 OR	Hs.443057	0.53	1.30	-	1.17	1.38	1.83
CD59_HUMAN: (CD59) C	Hs.75626	0.35	0.37	-	0.60	1.98	1.24
CD6: (CD6) T-CELL DI	Hs.278573	-	0.33	-	-	-	-
CD63: (CD63 OR MLA1)	Hs.436949	0.65	1.00	1.33	0.75	2.48	1.94
CD68: (CD68) MACROSI	Hs.445570	1.68	1.25	-	3.25	1.24	1.14
CD69: (CD69) EARLY A	Hs.246381	-	1.26	0.95	3.33	-	1.36
CD7: (CD7) T-CELL AN	Hs.82401	0.84	-	-	-	0.95	1.13
CD72: (LY-32 OR LYB-	Hs.36972	-	-	-	6.19	-	1.59
CD74: (CD74 OR DHLAG	Hs.116481	0.98	0.93	-	3.25	1.12	0.33
CD79A: (CD79A OR IGA	Hs.446471	1.37	0.94	-	1.93	1.54	1.78
CD79B: (CD79B OR IGB	Hs.79630	-	1.15	-	2.69	-	1.52
CD8: (CD8 OR CD28L	Hs.89575	-	-	-	1.56	-	1.53
CD81: (CD81 OR TAPA1	Hs.838	0.62	0.50	-	0.46	0.95	0.65
CD83: (CD83) ANTIGEN	Hs.54457	-	-	-	1.23	-	0.51
CD84: (CD84) LEUKOCY	Hs.79197	0.82	1.22	-	1.73	-	1.31
CD86: (CD86 OR CD28L	Hs.398093	1.14	-	-	6.72	-	1.51
CD8A: (CD8A OR MAL O	Hs.27954	0.92	1.77	-	-	0.89	1.15
CD8B: (CD8B OR LYT-3	Hs.85258	1.44	0.81	0.32	1.51	1.48	1.15
CD9: (CD9 OR MIC3) C	Hs.2299 Hs.405667	0.72	0.82	-	1.55	0.64	1.38
CD96: (TACTILE OR CD	Hs.387579	1.69	1.12	-	1.77	1.58	1.96
CD97: (CD97) LEUCOCY	Hs.142023	1.46	0.70	-	0.93	0.81	0.75
CDH3: (CDH3 OR CDHP)	Hs.3107	1.14	-	-	-	0.92	0.89
CDH5: (CDH5) VASCULA	Hs.191842	1.24	1.36	-	1.00	1.30	0.99
CDKN1A: (CDKN1A OR C	Hs.76206	-	-	-	1.50	-	-
CDKN1B: (CDKN1B OR K	Hs.370771	-	-	-	-	-	-
CDM: (BCAP31 OR BAP3	Hs.238990	0.58	0.52	-	0.53	1.33	0.41
CEA_HUMAN: (CEACAM5	Hs.381232	1.56	0.69	0.43	1.58	1.45	1.42
CEACAM1: (CEACAM1 OR	Hs.220529	-	-	-	0.38	-	0.53
CEBPB: (CEBPB OR TCF	Hs.512682	1.73	-	-	1.78	0.91	0.98
CEBPG: (CEBPG) CCAAT	Hs.99029	1.17	0.94	-	0.74	1.32	0.93
CFH: (HF1 OR HF OR C	Hs.2227	1.15	0.94	-	0.71	1.47	0.93
CGA: (CGA OR CGA1) G	Hs.278568	1.12	-	-	1.24	-	0.99
CHESS1: (CHES1) CHEC	Hs.119689	1.18	-	-	-	-	1.18
CIS4: (SOCS4 OR SOCS	Hs.211773	0.84	0.75	-	0.63	1.75	0.89
CISH: (CISH OR G18 O	Hs.8257	0.72	-	-	0.55	0.89	0.76

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CISH6: (SOCS5 OR CIS	Hs.355724	1.12	-	-	1.29	0.72	1.19
CLARP: (CFLAR OR CLA	Hs.436657	-	-	-	0.52	0.70	0.49
CLU: (CLU) CLUSTERIN	Hs.159553	0.11	2.20	-	0.75	0.87	1.44
CMKLR1: (CMKLR1 OR D	Hs.113207	0.97	-	-	2.37	-	0.96
CMKRL2: (CMKRL2 OR D	Hs.75110	-	-	-	0.73	0.98	1.98
CNR1: (CNR1 OR CNR)	Hs.524920	0.98	-	-	1.23	-	1.18
CNTF: (CNTF) CILIARY	Hs.179729	1.20	1.77	0.57	1.46	1.33	0.99
COL11A1: (COL11A1) C	Hs.439168	-	1.21	-	2.55	-	1.40
COL11A2: (COL11A2) C	Hs.390171	1.59	1.34	-	1.23	1.54	1.61
COL12A1: (COL12A1) C	Hs.101302	-	-	-	-	-	1.67
COL13A1: (COL13A1 OR	Hs.211933	-	-	-	-	-	1.11
COL15A1: (COL15A1) C	Hs.409034	0.76	-	-	1.23	-	0.91
COL16A1: (COL16A1) C	Hs.26208	0.90	-	-	1.22	-	1.29
COL17A1: (COL17A1) P	-	-	1.62	-	2.68	-	1.74
COL18A1_1: (COL18A1)	Hs.413175	0.66	0.85	-	0.23	0.78	0.55
COL18A1_2: (COL18A1)	Hs.413175	-	-	-	0.55	1.51	0.79
COL1A1: (COL1A1) C	Hs.172928	0.88	0.80	-	0.92	-	1.59
COL1A1: (COL1A1) COL	Hs.232115	16.32	1.37	-	5.22	1.13	0.95
COL1A2: (COL1A2) COL	Hs.408182	7.55	-	-	5.12	-	2.23
COL2A1: (COL2A1) COL	Hs.443625	1.33	1.39	-	1.47	1.28	1.00
COL3A1: (COL3A1) COL	Hs.437173	3.32	0.89	-	2.55	0.44	1.67
COL4A1: (COL4A1) COL	Hs.407912	1.13	0.82	0.97	0.78	0.94	0.89
COL4A2: (COL4A2) COL	Hs.407817	0.92	0.84	-	0.58	1.47	1.20
COL4A3: (COL4A3) COL	Hs.169825 Hs.497023	0.89	1.36	-	1.25	1.75	1.62
COL4A5: (COL4A5) COL	Hs.408	1.58	1.34	-	0.89	1.28	0.92
COL4A6: (COL4A6) COL	Hs.433695	0.92	-	-	-	-	0.98
COL5A1: (COL5A1) PRO	Hs.283393	2.43	-	-	1.82	0.97	1.19
COL5A2: (COL5A2) COL	Hs.415997	2.94	0.86	-	0.92	1.45	0.84
COL6A1: (COL6A1) COL	Hs.420269	2.26	1.19	-	0.32	0.86	0.54
COL6A2: (COL6A2) COL	Hs.233240	5.44	-	-	0.92	1.19	0.54
COL6A3: (COL6A3) COL	Hs.1640	-	1.14	-	2.00	-	1.15
COL7A1: (COL7A1) COL	Hs.114599	0.47	0.98	-	0.67	0.90	0.76
COL8A1: (COL8A1) COL	Hs.353001	1.64	-	-	1.34	-	1.17
COL8A2: (COL8A2) COL	Hs.149809	1.46	-	-	1.74	1.56	1.34
COL9A1_1: (COL9A1) C	Hs.418012	1.70	-	-	2.86	0.99	1.63
COL9A2: (COL9A2) COL	Hs.126248	0.97	0.95	-	0.64	1.22	0.86
COL9A3: (COL9A3) ALP	Hs.1584	1.33	1.27	-	1.43	1.46	1.11
COP1: (COP1) COP1 PR	Hs.412957	0.94	-	-	0.44	0.74	1.23
CR1-CR1L: (CR1 OR C3	Hs.334019 Hs.89688	0.83	-	-	-	-	0.96
CR2: (CR2 OR C3DR) C	Hs.73792	-	1.32	-	-	-	0.96
CREB1: (CREB1) CAMP-	Hs.22315	0.74	-	-	-	0.87	0.88
CREBPA: (CREB1 OR CR	Hs.149	1.14	-	-	-	0.92	0.92
CREB-RP: (CREBL1 OR	Hs.42853	0.92	-	0.54	-	0.83	1.49
CREL: (REL) C-REL PR	Hs.44313	0.79	-	-	-	0.92	0.86
CREM: (CREM) CAMP RE	Hs.231975	0.69	1.66	-	0.67	0.77	0.99
CRK: (CRK) PROTO-ONC	Hs.511822	0.83	-	-	0.69	1.19	1.12
CRKL: (CRKL) CRK-LIK	Hs.5613	1.54	-	-	1.39	1.32	-
CSF1: (CSF1 OR CSFM)	Hs.173894	-	-	-	-	-	1.15
CSF1R: (CSF1R OR CSF	Hs.174142	-	-	-	-	-	1.51
CSF2RA: ((CSF2RAX OR	Hs.520937	1.83	1.55	0.86	1.95	1.42	0.92
CSF2RB: (CSF2RB OR I	Hs.285401	1.17	0.66	-	0.95	1.36	0.72
CSF3: (CSF3) GRANULO	Hs.2233	2.00	1.19	-	0.43	1.53	0.93
CSF3R: (CSF3R OR GCS	Hs.381027	1.21	1.14	-	1.29	1.26	0.84
CSK: (CSK) TYROSINE-	Hs.77793	1.52	-	-	1.25	1.15	-
CTGF: (CTGF OR HCS24	Hs.434488	0.91	-	-	0.75	0.26	0.53
CTLA4: (CTLA4 OR CD1	Hs.410037	1.53	-	-	2.53	-	1.26
CTSD: (CTSD) CATHEPS	Hs.247824	-	-	-	2.16	0.49	0.55
CX3CL1: (SCYD1 OR FK	Hs.343475	0.96	0.88	0.57	0.75	1.24	0.88
CX3CR1: (CX3CR1 OR G	Hs.80420	0.80	-	-	2.82	-	1.53
CXCL1: (SCYB1 OR I	Hs.78913	1.19	1.16	-	2.19	1.34	1.46
CXCL11: (SCYB11 OR S	Hs.413924	0.84	0.85	-	1.31	1.33	1.32
CXCL12: (SDF1) STROM	Hs.103982	1.43	-	-	0.33	0.53	0.52
CXCL13: (BLC OR BCA1	Hs.436042	1.13	0.59	-	0.64	1.58	0.92
CXCL14: (SCYB14 OR N	Hs.100431	0.22	0.46	0.64	0.17	1.31	0.38
CXCL16: (911K24R	Hs.24395	0.92	-	-	2.58	1.34	1.26
CXCL6_HUMAN: (CXCL6	Hs.82407	0.84	0.59	0.77	0.64	1.23	1.64
CXCL7: (SCYB7 OR PPB	Hs.164021	1.99	0.72	-	1.19	1.32	0.99
CXCR4: (CXCR4 OR LES	Hs.198252	0.20	0.58	-	14.66	0.47	1.52
CYPA: (PPIA OR CYPA)	Hs.421986	0.99	0.97	0.59	0.49	2.13	2.34
CYR61: (CYR61 OR IGF	Hs.356331	1.59	0.51	-	0.24	0.76	0.38
DAF: (DAF OR CR OR C	Hs.8867	0.76	1.22	-	1.47	0.54	1.50
DAPK1: (DAPK1 OR DAP	Hs.408864	0.96	-	-	-	1.75	0.93
DAPK2: (DAPK2) DEATH	Hs.244318	0.96	-	-	1.71	-	0.97
DCIR_HUMAN: (DCIR) D	Hs.129208	0.73	-	-	2.83	-	1.77
DCP1: (DCP1 OR DCP O	Hs.115515	1.37	0.92	-	1.25	1.46	0.97
DDR1: (EDDR1 OR CAK	Hs.156316	0.32	0.63	-	0.14	1.43	2.28
DDR3: (TNFRSF25 OR T	Hs.298469	1.16	1.22	0.55	1.19	1.46	0.89
DLL1: (DLL1) DELTA-L	Hs.423573	1.46	1.38	0.95	1.37	1.33	1.72
DPP4: (DPP4 OR ADCP2	Hs.440905	0.57	1.33	-	0.75	0.56	0.47
DR6: (TNFRSF21 OR DR	Hs.368657	0.97	0.79	-	-	1.68	0.85
E2F1: (E2F1 OR RBBP3	Hs.44926	1.38	0.65	-	0.43	1.55	0.68
E2F5: (E2F5) TRANSCR	Hs.159651	0.89	-	-	0.92	1.13	1.17

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E4BP4: (IL3BP1 OR E4	Hs.96055	1.45	1.54	-	0.79	1.13	0.92
EBCTF: (EBF) EARLY B	Hs.447905	0.87	1.10	-	0.91	0.90	0.86
EBI2: (EBI2) EBV-IND	Hs.79334	0.54	1.20	-	6.53	1.45	1.32
ECE1: (ECE1) ENDOTHE	Hs.120785	1.99	0.89	-	1.60	1.17	1.15
ECE2: (ECE2) ENDOTHE	Hs.784	1.25	-	-	1.25	0.88	1.77
ECT2: (ECT2) ECT2 PR	Hs.232688	-	-	-	-	-	1.24
EGR1: (EGR1 OR ZNF22	Hs.129801	1.52	-	-	1.18	1.27	0.77
EGR2: (EGR2 OR KROX2	Hs.293257	1.20	-	-	0.60	0.92	0.78
EGR3: (EGR3 OR PILOT	Hs.326035	0.98	-	-	0.79	0.95	0.84
EMR1: (EMR1) CELL SU	Hs.1395	1.26	-	0.46	1.23	0.99	-
ENG: (ENG OR END) EN	Hs.74088	1.17	0.87	0.39	0.27	0.73	0.87
ENIGMA: ENIGMA PROTE	Hs.2375	1.75	-	-	0.74	1.15	0.49
ENOS: (NOS3) NITRIC-	Hs.76753	1.89	0.82	-	0.94	1.26	0.85
EPHB2: (EPHB2 OR EPT	Hs.436339	1.82	1.25	-	0.66	0.99	0.88
EPOR: (EPOR) ERYTHRO	Hs.446303	0.89	-	-	0.48	1.15	0.80
ESR1: (ESR1 OR NR3A1	Hs.125124	1.45	0.94	-	1.30	1.21	0.81
ESR2: (ESR2 OR NR3A2	Hs.127826	0.98	0.94	-	0.53	1.16	1.69
ETS1: (ETS1) C-ETS-1	Hs.1657	1.66	-	-	0.42	0.99	0.74
ETS2: (ETS2) C-ETS-2	Hs.443150	1.26	0.50	-	1.18	1.27	0.75
F2R: (F2R OR PAR1 OR	Hs.18063	1.18	0.82	0.50	-	-	0.98
F3: (F3 OR CF3 OR CF	Hs.292477	1.27	0.75	-	1.34	-	0.58
FADD: (FADD OR MORT1	Hs.128087	1.28	-	-	1.15	1.39	1.34
FAIM: (FAIM) FAS APO	Hs.62192	0.63	0.99	0.74	0.42	1.31	0.95
FAK1: (FAK1 OR FAK O	Hs.86131	1.55	0.78	-	0.87	0.54	1.42
FAST1: (FOXH1 OR FAS	Hs.173438	1.27	-	-	1.68	1.27	0.97
FBLN1_1: (FBLN1) FIB	Hs.434281	1.74	0.82	-	0.99	0.86	0.96
FBLN2: (FBLN2) FIBUL	Hs.159251	1.19	0.85	-	1.28	0.49	0.83
FBXW1B: (FBXW1B OR F	Hs.445240	-	0.97	-	1.36	-	0.92
FBXW2: (FBXW2 OR FBW	Hs.198862	1.26	0.86	-	0.62	1.16	1.16
FCER2: (FCER2 OR IGE	Hs.226434	1.18	1.58	-	1.58	-	0.87
FCGR1A: (FCGR1A OR F	Hs.280385	2.97	0.98	-	15.40	1.47	1.39
FCGR2_HUMAN: (FCGR2A	Hs.444354	1.12	-	-	36.78	1.65	1.49
FCP1: (FCP1) SERINE	Hs.1416	1.17	0.96	-	0.63	0.79	1.53
FGR: (FGR OR SRC2) P	Hs.77424 Hs.516104	0.94	-	-	1.89	1.26	0.74
FIBRILLIN1: (FBN1 OR	Hs.352642 Hs.126384	1.76	1.16	-	0.88	0.54	1.22
FIBRILLIN2: (FBN2) F	Hs.4076	-	-	-	-	-	1.27
FIBROMODULIN: (FMOD	Hs.1422	1.25	0.51	-	1.39	1.35	0.99
FIP2: (FIP2 OR NEMO2	Hs.750	1.13	0.98	-	0.28	0.92	1.18
FKHL16: (FOXM1 OR FK	Hs.79432	0.96	0.32	-	1.38	-	0.68
FKHR: (FOXO1A OR FKH	Hs.442844	0.48	0.90	-	0.43	0.93	1.91
FKHRL1: (FOXO3A OR F	Hs.390162	0.88	-	-	0.48	1.42	0.60
FLAP: (ALOX5AP OR FL	Hs.239 Hs.479302 Hs.511941	1.26	-	-	1.77	1.68	0.94
FLASH: (CASP8AP2 OR	Hs.170133	1.13	0.99	-	0.59	1.52	1.98
FLASHLIKE: FLASH REL	Hs.14845	0.91	1.59	-	0.86	1.32	0.86
FLT3: (FLT3 OR STK1	Hs.100194	-	1.00	-	-	-	0.89
FLT3LG: (FLT3LG) SL	Hs.122843	0.86	1.96	-	0.97	0.99	1.18
FN1: (FN1 OR FN) FIB	Hs.279763 Hs.201550	7.46	-	-	6.47	0.56	1.46
FOS_1: (FOS) P55-C-F	Hs.385	0.98	1.43	-	0.38	0.65	1.47
FOSB: (FOSB OR GS3)	Hs.428	1.45	-	-	1.42	1.29	0.67
FOXG1A-FOXG1B: (FOXG	Hs.418138	1.16	0.88	0.32	0.64	1.12	1.69
FRA1: (FOSL1 OR FRA1	Hs.25647	0.78	0.49	-	2.38	0.82	0.92
FRA2: (FOSL2 OR FRA2	Hs.75678	6.66	1.37	0.42	4.28	1.85	1.90
FRAP: (FRAP) FKBP-RA	Hs.283565	1.65	0.61	0.20	-	0.82	7.37
FTH: (FTH1 OR FTH OR	Hs.301612	2.28	-	-	1.25	2.51	0.94
FUT3: (FUT3 OR LE) G	Hs.386249 Hs.525266 Hs.169277	0.98	2.37	0.72	0.34	1.12	1.33
FYN: (FYN) PROTO-ONC	Hs.439387	0.45	-	-	-	0.90	-
G22P1: (G22P1) ATP-D	Hs.338207	0.85	-	-	0.34	0.63	0.87
GADD153: (DDIT3 OR C	Hs.448738	0.87	0.55	-	0.55	1.53	0.79
GADD34: (GADD34) APO	Hs.169238	1.37	0.36	-	0.84	1.43	0.89
GADD45: (GADD45A OR	Hs.390567	0.67	0.92	0.65	0.16	0.70	0.90
GAPD: (GAPD) (GAPDH)	Hs.169744	1.95	1.33	-	0.63	4.26	0.48
GAS2: (GAS2) GROWTH-	Hs.392171 Hs.355867	-	1.15	0.76	-	-	-
GAS3: (PMP22 OR GAS3	Hs.76556	1.23	1.30	-	2.12	0.89	1.46
GATA3: (GATA3) TRANS	Hs.80409	1.34	-	-	-	0.99	1.92
GATA4_HUMAN: (GATA4)	Hs.169476	1.12	-	-	0.42	0.93	0.59
GDIA1: (ARHGDIA OR G	Hs.135665	2.36	0.66	-	0.33	1.25	0.68
GEM: (GEM OR KIR) GT	Hs.372031	0.69	0.58	-	0.99	0.77	0.54
GG2-1: (GG2-1 OR MDC	Hs.169946	0.73	-	-	0.74	0.96	0.97
GITRL: (TNFSF18 OR A	Hs.243987	1.57	-	-	0.53	1.60	1.16
GL5: (GL5) B7-LIKE	Hs.159161	0.78	-	-	-	0.95	0.83
GM-CSF: (CSF2 OR GMC	Hs.79022	0.97	1.33	-	-	-	1.11
GN6ST: (GN6ST OR CHS	Hs.17839	0.82	0.42	-	1.58	0.82	1.17
GP1BA: (GP1BA) PLATE	Hs.248197	1.18	0.74	0.68	1.33	1.38	1.23
GP9: (GP9) PLATELET	Hs.1349	1.27	1.17	-	1.27	1.14	0.89
GPCR25: (GPCR25 OR T	Hs.8786	-	-	-	3.52	-	1.41
GPR17: (GPR17) PUTAT	Hs.1472	0.79	-	-	1.78	0.94	1.14
GPR31: (GPR31) PROBA	Hs.1144	1.35	-	-	1.60	1.42	1.16
GPR5: (CCXCR1 OR XCR	Hs.131924	1.25	-	-	1.59	1.26	1.18
GRAIL: (GRAIL) CDNA:	Hs.46453	0.60	-	-	-	0.91	0.84
GRB1: (GRB1) GROWT	Hs.248124	0.95	-	-	1.47	1.65	1.20
GRB2: (GRB2 OR ASH)	Hs.248116	0.80	0.68	0.43	1.80	0.98	1.44
GRL: (GRL OR NR3C1)	Hs.512118	1.26	0.76	0.59	1.48	1.83	1.96

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GRO1_HUMAN: (CXCL1 O	Hs.411366	0.30	0.78	-	-	0.70	1.22
GRO2_HUMAN: (CXCL2 O	Hs.126608	0.81	0.58	-	0.67	1.33	0.86
GSTM1: (GSTM1 OR GST	Hs.789	0.28	-	-	0.23	1.98	-
GZMB: (GZMB OR CTLA1	Hs.75765	-	-	-	2.82	-	-
HCK: (HCK) TYROSINE-	Hs.301961 Hs.279837 Hs.348387	1.14	0.64	-	1.95	1.24	0.94
HES1: (HES1 OR HRY O	Hs.1051	0.50	-	-	0.25	1.85	0.63
HEVIN: (HEVIN) HIGH	Hs.89555	0.15	0.26	-	0.29	0.58	0.62
HEXA: (HEXA) BETA-HE	Hs.250666	0.95	-	-	0.48	0.76	0.73
HFH4: (FOXJ1 OR FKHL	Hs.75445	1.37	1.17	-	0.97	1.19	0.93
HGF: (HGF OR HPTA) H	Hs.411157 Hs.513009	1.13	1.58	-	1.29	1.45	1.48
HGFALIKE: (HGFALIKE)	Hs.370041	0.80	1.55	-	0.68	0.97	1.87
HHAVCR-1: (HHAVCR-1	Hs.396530	1.29	-	-	1.49	1.49	1.19
HHEX: (HHEX OR PRHX	Hs.422542	1.28	1.53	0.68	1.32	1.39	1.12
HIF1A: (HIF1A) HYPOX	Hs.129711	2.99	0.88	1.19	1.45	1.11	1.86
HJ1: (JAG1) JAGGED 1	Hs.118651	1.16	1.29	-	1.23	1.12	1.13
HJ2: (HJ2 JAGGED2) N	Hs.412416	1.24	0.60	-	1.54	1.27	2.57
HLA-DQA_HUMAN: (HLA-	Hs.409202	0.70	-	-	6.80	0.89	1.61
HLF: (HLF) HEPATIC L	Hs.387679 Hs.289095	-	-	-	-	-	1.25
HLX1: (HLX1) HOMEOBO	Hs.250692	1.18	1.22	0.60	1.42	1.18	1.28
HMOX1: (HMOX1 OR HO1	Hs.74870	2.27	0.76	-	1.12	1.34	0.85
HMOX2: (HMOX2 OR HO2	Hs.202833	0.97	-	-	0.46	0.99	1.14
HNF3A: (FOXA1 OR HNF	Hs.284279	0.83	0.99	-	1.46	0.99	1.87
HNF3B: (FOXA2 OR HNF	Hs.70604 Hs.163484	1.84	-	-	0.76	0.99	1.13
HNF3G: (FOXA3 OR TCF	Hs.155651	0.92	0.87	-	1.13	-	0.98
HPRT: (HPRT1 OR HPRT	Hs.36137	1.74	1.33	-	1.76	1.25	1.12
HR2R: (HH2R) HISTAMI	Hs.412707	-	-	-	1.41	-	0.76
HRAS: (HRAS) HRAS SU	Hs.247885	0.78	0.69	0.45	0.96	1.25	1.11
HRAS1: (HRAS1 OR HRA	Hs.36761	1.43	-	-	0.49	1.16	1.25
HRH1: (HRH1) HISTAMI	Hs.37003	1.30	0.37	0.42	1.39	1.21	0.72
HSC73: (HSPA8 OR HSP	Hs.1570	1.59	0.82	0.66	0.30	1.22	0.79
HSF4: (HHSF4) HEAT S	Hs.180414	0.78	1.15	-	-	-	0.97
HSP15: (HSP15 OR H	Hs.75486	1.91	0.67	0.29	0.44	0.98	3.93
HSP7.2: (HSPA2 OR H	Hs.36927	1.77	0.53	-	2.49	1.45	0.45
HSPA1A: ((HSPA1A OR	Hs.432648	0.46	-	-	0.22	0.64	1.51
HSPA1L: (HSPA1L) HEA	Hs.75452 Hs.274402	0.83	0.74	-	-	0.82	1.39
HSPA4: (HSPA4 OR HSP	Hs.80288	0.81	1.26	-	0.42	1.27	-
HSPA6-HSPA7: (HSPA6	Hs.90093	0.86	0.52	-	1.48	1.14	0.81
HSPA9: (HSPA9B OR HS	Hs.3268	0.82	0.43	0.31	0.20	0.99	0.65
HSPCA: (HSPCA OR HSP	Hs.184233	0.69	0.66	-	0.93	1.62	0.69
HSPD1: (HSPD1 OR HSP	Hs.446579	0.71	0.57	-	0.13	0.74	1.00
HSPG2: (HSPG2) BASEM	Hs.79037	5.88	-	-	3.44	0.67	1.89
HSR.1: (HSP7-4 OR H	Hs.211573 Hs.470489	0.72	-	-	0.85	1.60	1.14
HTLF: (HTLF) HUMAN T	Hs.430666	1.16	-	-	0.94	0.93	1.16
HTRIP: (HTRIP OR TRA	Hs.103126	0.97	-	-	-	-	-
IAP1: (BIRC2 OR API1	Hs.127799	21.24	0.95	0.74	1.34	0.57	-
IAP2_1: (BIRC3 OR AP	Hs.49215	16.29	-	-	0.62	1.36	1.14
IAP4_2: (BIRC5 OR AP	Hs.386467	0.71	-	-	-	1.38	1.12
IBSP: (IBSP OR BNSP)	Hs.433303	-	-	-	-	-	1.49
ICAM1: (ICAM1 OR ICA	Hs.353214	-	0.93	0.66	-	-	0.85
ICAM2: (ICAM2 OR ICA	Hs.56247	1.48	1.22	-	0.95	1.35	1.17
ICAM3_HUMAN: (ICAM3)	Hs.14155	3.70	-	-	1.28	2.15	0.90
ICOS: (ICOS) ACTIVAT	Hs.391392	1.45	-	-	0.48	0.99	-
ID4: (ID4) DNA-BINDI	Hs.415359	1.22	0.80	0.66	1.22	1.27	1.20
IDD: (IDD OR DGCR2 O	Hs.20315	-	-	-	-	-	1.21
IFIT1: (IFIT1 OR IFI	Hs.458414	0.52	0.55	-	0.26	0.81	1.31
IFITM1_HUMAN: (IFITM	Hs.174195 Hs.374650	0.21	0.89	-	1.31	0.28	0.54
IFITM2-IFITM3_HUMAN:	Hs.37026	0.56	0.22	-	1.34	0.94	0.81
IFNA1_HUMAN: (IFNA1	Hs.211575	-	-	-	-	0.97	0.85
IFNA2_HUMAN: (IFNA2)	Hs.181315	0.88	0.74	-	1.36	0.98	1.28
IFNAR1: (IFNAR1 OR I	Hs.86958 Hs.512211	1.75	1.75	1.18	1.17	1.21	1.20
IFNAR2: (IFNAR2 OR I	Hs.93177	1.49	-	-	0.53	1.25	0.83
IFNB1: (IFNB1 OR IFN	Hs.856	1.29	1.62	0.76	1.32	1.40	0.99
IFNG: (IFNG) INTERFE	Hs.180866	1.45	-	-	3.12	1.12	1.59
IFNGR1: (IFNGR1 OR I	Hs.409200	0.95	-	-	3.32	0.73	1.85
IFNGR2: (IFNGR2 OR I	Hs.349109	1.35	-	-	3.47	1.30	1.18
IGF2: (IGF2) INSULIN	Hs.401316	1.12	0.69	0.52	1.85	1.44	-
IGFBP1: (IGFBP1 OR I	Hs.274313	1.19	0.86	-	1.38	1.33	1.24
IGFBP6: (IGFBP6 OR I	Hs.31323	0.45	-	-	0.98	2.26	7.43
IKAP: (IKAP OR IKBKA	Hs.81328	1.00	0.53	-	0.65	0.96	1.83
IKBA: (NFKBIA OR NFK	Hs.9731	0.39	0.94	-	0.45	0.65	0.87
IKBB: (NFKBIB OR IKB	Hs.458276	1.37	0.82	-	0.60	1.68	0.67
IKBE: (NFKBIE OR IKB	Hs.198998	0.87	-	-	1.18	0.59	0.99
IKBR: (NFKBIL2) IKAP	Hs.413513	1.23	0.67	0.67	0.55	1.13	0.89
IKKA: (IKK ALPHA OR	Hs.43505	0.96	1.27	-	0.74	0.93	0.95
IKKB: (IKKB OR IKBKB	Hs.193717	1.56	-	-	0.88	0.93	0.96
IKKG: (IKBKG OR NEMO	Hs.327	-	-	-	0.65	0.94	0.90
IL11: (IL11) INTERLE	Hs.418291	-	0.74	0.23	2.35	-	1.34
IL12A: (IL12A OR NKS	Hs.1721	-	0.41	-	2.41	-	1.21
IL12B: (IL12B OR NKS	Hs.673	0.89	-	-	1.90	1.14	1.15
IL12RB1: (IL12RB1 OR	Hs.674	1.52	-	-	-	0.97	0.88
IL12RB2: (IL12RB2) I	Hs.223894	0.94	-	-	-	0.88	1.75
IL13: (IL13 OR NC3	Hs.413608	1.16	1.15	0.63	1.74	1.43	1.18

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IL13RA1: (IL13RA1 OR	Hs.845	0.73	-	-	1.26	1.13	1.14
IL14: (IL14) HYPOTHE	Hs.285115	1.48	1.32	-	1.29	1.40	1.34
IL15_3_HUMAN: (IL15)	Hs.168132	0.77	-	-	0.98	-	0.80
IL16: (IL16) INTERLE	Hs.170359	1.27	0.86	0.71	2.38	1.34	1.18
IL17: (IL17 OR CTLA8	Hs.41724	1.43	-	-	2.77	1.15	1.58
IL17F: (IL17F OR IL2	Hs.272295	0.84	0.71	-	1.65	0.86	1.11
IL17R: (IL17R) INTER	Hs.129751	0.83	-	-	1.14	1.26	1.12
IL18: (IL18 OR IGIF)	Hs.83077	1.65	-	-	1.27	1.27	1.73
IL18BP: (IL18BP) INT	Hs.325978	1.16	-	-	2.00	0.99	0.92
IL18R1: (IL1RRP OR I	Hs.159301	0.84	-	-	-	0.98	1.10
IL1A: (IL1A) INTERLE	Hs.1722	0.87	1.18	-	1.10	1.17	0.94
IL1B: (IL1B) INTERLE	Hs.126256	-	-	-	1.36	0.83	1.49
IL1R: (IL1RA OR IL	Hs.82112	1.27	-	-	5.79	0.93	1.88
IL1R1: (IL1R1 OR IL1	Hs.25333	0.72	-	-	-	0.72	1.83
IL1R2: (IL1R2 OR IL1	-	1.13	-	-	1.28	-	1.55
IL1RAP: (IL1RAP) IL-	Hs.66	0.89	0.92	-	0.90	1.15	0.90
IL1RB: (IL1RB OR C	Hs.66	1.16	0.82	0.70	0.95	0.93	0.85
IL1RL1: (IL1RL1 OR S	Hs.416814	0.65	-	-	-	0.99	-
IL1RL2: (IL1RL2 OR I	Hs.81134	1.12	0.87	0.51	1.59	1.17	-
IL1RN: (IL1RN OR IL1	Hs.89679	-	0.91	0.58	4.26	-	0.94
IL2: (IL2 OR IL-2) I	Hs.302014	-	-	-	-	-	1.65
IL21: (IL21) INTERLE	Hs.210546	-	-	-	-	-	1.38
IL21R: (IL21R OR NIL	Hs.110915	1.85	-	-	1.63	0.92	0.81
IL22R: (IL22R) IL-22	Hs.130058	-	-	-	-	-	1.18
IL2RA: (IL2RA OR IL2	Hs.75596	1.25	0.83	-	-	-	0.97
IL2RB: (IL2RB) INTER	Hs.84	0.46	1.15	-	-	0.69	1.15
IL2RG: (IL2RG) CYTOK	Hs.694	0.56	-	-	7.96	-	0.88
IL3: (IL3 OR IL-3 OR	Hs.460433	1.25	-	-	1.23	1.56	1.13
IL3RA: ((IL3RAX OR I	Hs.73917	-	1.93	0.72	1.52	-	0.98
IL4: (IL4 OR IL-4) I	Hs.75545	-	-	-	-	-	1.31
IL4R: (IL4R OR IL4RA	Hs.2247	-	1.70	-	1.54	-	1.29
IL5: (IL5 OR IL-5) I	Hs.68876	1.18	1.17	-	1.45	1.54	1.13
IL5RA: (IL5RA OR IL5	Hs.512234	0.99	0.38	-	2.27	-	1.98
IL6: (IL6 OR IFNB2 O	Hs.193400	-	-	-	2.89	-	1.54
IL6R: (L6RA OR IL6R)	Hs.71968	-	0.48	0.20	1.41	-	1.17
IL6ST: (IL6ST) INTER	Hs.72927	1.14	0.96	-	1.22	1.51	1.32
IL7: (IL7 OR IL-7) I	Hs.362807	-	0.99	0.71	1.54	-	1.47
IL7R: (IL7R) INTERLE	Hs.624	-	-	-	1.74	-	1.15
IL8_HUMAN: (IL8) INT	Hs.194778 Hs.846	-	-	-	4.35	-	1.43
IL8RA-IL8RB: (IL8RA	Hs.846 Hs.194778	-	0.70	-	1.52	-	1.35
IL8RB-IL8RA: (IL8RB	Hs.960	0.93	-	-	1.26	1.22	1.37
IL9: (IL9) INTERLEUK	Hs.407506	0.86	1.32	-	1.62	1.15	1.14
ILF: (ILF1 OR ILF) I	Hs.727	1.80	0.74	-	1.74	1.29	1.43
INHA: (INHA) INHIBIN	Hs.1735	-	0.89	-	-	-	1.54
INHBA: (INHBA) INHIB	Hs.374664	3.19	-	-	3.89	-	1.14
INHBB: (INHBB) INHIB	Hs.334575	1.37	-	-	0.97	1.42	1.30
INHBC: (INHBC) INHIB	Hs.439046	0.93	1.39	-	1.36	-	1.00
INOS: (NOS2A OR NOS2	Hs.1742	1.30	0.90	-	1.59	1.34	1.11
INTEGRINA7: (ITGA7)	Hs.373980	1.68	0.63	-	1.37	1.26	1.17
INTEGRINA8: (ITGA8)	Hs.182018	1.47	1.64	-	1.40	1.49	1.12
INTEGRINA9: (ITGA9)	Hs.424542	1.98	-	-	0.92	1.39	0.96
INTEGRINB5: (ITGB5)	Hs.142295	1.12	0.77	-	0.63	1.11	0.83
INTEGRINB6: (ITGB6)	Hs.268552	0.59	-	-	0.95	0.74	1.10
INTEGRINB7: (ITGB7)	Hs.80645	0.61	-	-	0.77	0.95	0.77
INTEGRINB8: (ITGB8)	Hs.75254	0.68	-	-	-	1.28	0.89
IP4P-BII: INOSITOL P	Hs.334450	0.99	-	-	0.64	0.97	1.80
IPLA2: (IPLA2) CALCI	Hs.355827	0.65	1.50	-	0.43	0.83	1.26
IQGAP1: (IQGAP1) RAS	Hs.166120	1.56	0.65	0.30	1.66	1.17	1.63
IQGAP2: (IQGAP2) RAS	Hs.314676	0.77	-	-	-	0.65	1.57
IRAK1: (IRAK1 OR IRA	Hs.439320	0.90	-	-	1.67	0.77	0.69
IRAK2: (IRAK2) INTER	Hs.158237	0.83	0.92	-	-	0.87	0.65
IRAK-4: (IRAK-4) (LO	Hs.387725	1.57	-	-	1.47	1.20	0.90
IRAK-M: (IRAK-M) IL-	Hs.411312	-	-	-	-	-	0.92
IRF1: (IRF1) INTERFE	Hs.265829	0.84	0.83	-	1.12	0.87	0.69
IRF3: (IRF3) INTERFE	Hs.145140	1.30	-	-	0.48	1.74	1.96
IRF5: (IRF5) INTERFE	Hs.149609	1.14	0.72	-	1.49	0.82	1.38
IRF6: (IRF6) INTERFE	Hs.212296	0.79	-	-	1.17	1.00	0.87
IRF7: (IRF7) INTERFE	Hs.74369 Hs.51483	0.99	-	-	1.74	0.96	1.90
ITCH: (AIP4 OR ITCH)	Hs.171025	0.98	0.88	-	0.96	1.49	0.93
ITGA1_2: (ITGA1) INT	Hs.222	0.73	1.24	-	0.99	-	0.97
ITGA1_HUMAN: (ITGA1	Hs.389133	1.53	-	-	1.20	1.27	1.29
ITGA2: (ITGA2) INTEG	Hs.174103	0.82	-	-	1.51	1.44	0.77
ITGA2B: (ITGA2B OR I	Hs.172631	0.68	0.83	-	-	0.87	1.18
ITGA3: (ITGA3) INTEG	Hs.436873	1.56	-	-	1.85	1.36	-
ITGA4: (ITGA4 OR VLA	Hs.385521 Hs.381264	-	-	-	-	-	0.92
ITGA5: (ITGA5 OR FNR	Hs.287797	0.97	1.92	-	1.96	0.88	1.85
ITGA6: (ITGA6) INTEG	Hs.375957	-	0.75	0.52	1.58	-	1.52
ITGAE: (ITGAE) INTEG	Hs.87149	0.59	-	-	1.34	1.53	1.22
ITGAL: (ITGAL OR CD1	Hs.85266	0.68	1.45	-	0.77	0.98	1.25
ITGAM: (ITGAM OR CR3	Hs.149846	-	1.17	-	2.84	-	1.19
ITGAV: (ITGAV OR VNR	Hs.57664	1.46	0.79	-	1.52	1.55	1.38
ITGAX-ITGAD_HUMAN: (	Hs.1741	1.20	-	-	1.44	1.48	1.33

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ITGB1: (ITGB1 OR FNR	Hs.355722	4.31	2.33	-	0.65	0.43	0.79
ITGB2: (ITGB2 OR CD1	Hs.420257	1.78	0.82	1.88	5.60	1.22	1.14
ITGB3: (ITGB3 OR GP3	Hs.76716	0.69	-	-	0.63	1.36	0.98
ITGB4: (ITGB4) INTEG	Hs.76415	1.52	-	-	1.18	1.00	-
ITIH1: (ITIH1 OR IGH	Hs.211576	1.68	0.71	0.73	0.77	1.23	0.90
ITIH3: (ITIH3) INTER	Hs.66392	0.96	-	-	-	1.00	0.89
ITIH4: (ITIH4 OR IHR	Hs.433445	1.84	0.40	-	0.45	1.49	0.87
ITK: (ITK OR LYK OR	Hs.436004	0.54	-	-	-	1.30	1.45
ITSN: (ITSN) INTERSE	Hs.434374	0.92	-	-	1.30	-	1.16
JAK1: (JAK1 OR JAK1A	Hs.210387	1.32	-	-	2.12	0.67	-
JAK2: (JAK2) TYROSIN	Hs.247700	1.32	0.78	-	1.34	1.17	1.33
JAK3: (JAK3) TYROSIN	Hs.78465	1.63	0.90	-	0.55	1.16	1.33
JM2: (FOXP3 OR IPEX)	Hs.400124	1.29	0.56	-	1.31	1.37	0.81
JUN: (JUN) TRANSCRIP	Hs.323949	0.75	1.31	-	0.18	0.63	0.89
JUNB: (JUNB) TRANSCR	Hs.80976	0.87	0.52	0.62	0.47	0.65	0.65
KAI1: (KAI1 OR CD82	Hs.86998	1.35	0.49	-	0.95	1.31	1.24
KI67: (MKI67) ANTIGE	Hs.81665	1.35	0.63	-	1.43	1.29	0.71
KIAA827: (NFAT5 OR	Hs.1048	1.41	0.94	-	1.32	1.32	0.94
KIT: (KIT OR SL) MAS	Hs.268510 Hs.387787	0.90	0.77	-	1.53	1.13	1.68
KITLG: (KITLG OR MGF	Hs.41682	0.76	0.92	-	-	0.87	1.31
KLRC4: (KLRC4 OR NKG	Hs.77741	0.99	-	-	1.24	0.89	1.46
KLRD1: (KLRD1 OR CD9	Hs.8878	1.37	-	-	1.55	1.48	0.89
KNG-KNT1-KNT2: (KNG)	Hs.276238	-	1.00	0.63	-	-	1.74
KNSL1: (KNSL1 OR EG5	Hs.445201	1.19	-	-	1.30	1.19	-
KSR1: (KSR1 OR HB) K	Hs.409523	0.92	1.61	-	-	-	1.28
L1CAM: (L1CAM OR CAM	Hs.500930 Hs.270364	-	-	-	1.36	-	0.95
LAG3: (LAG3 OR FDC)	Hs.445120	0.76	-	-	0.73	0.93	1.23
LAMA1: (LAMA1 OR LAM	Hs.83450	1.14	-	-	-	0.96	0.93
LAMA2: (LAMA2 OR LAM	Hs.437536	0.50	1.25	-	1.18	0.76	1.00
LAMA3: (LAMA3) LAMIN	Hs.11669	1.39	-	-	1.27	1.38	1.12
LAMA4: (LAMA4) LAMIN	Hs.122645	2.45	0.87	-	1.69	0.95	1.33
LAMA5: (KIAA533 OR	Hs.436983	0.93	-	-	0.37	0.98	0.95
LAMB1: (LAMB1) LAMIN	Hs.432855	1.28	0.68	-	0.98	1.37	0.74
LAMB3: (LAMB3) LAMIN	Hs.69954	0.79	0.90	-	0.37	0.85	1.58
LAMG1: (LAMC1 OR LAM	Hs.150101	0.97	1.49	-	0.55	1.26	0.69
LAMG3: (LAMC3) LAMIN	Hs.232432	1.17	1.45	-	0.45	1.19	2.62
LAMP1: (LAMP1 OR LAM	Hs.209983	1.16	0.60	-	0.33	0.74	0.78
LAMP2: (LAMP2 OR LAM	Hs.498997	0.65	-	-	0.48	1.29	0.71
LAP18: (LAP18 OR OP1	Hs.294584	1.83	0.93	0.72	0.92	1.24	0.86
LAT: (LAT) TYROSINE	Hs.154078	-	-	-	2.53	1.00	1.85
LB4D: (LTB4DH OR DIG	Hs.1765	0.52	-	-	0.12	0.89	1.16
LBP: (LBP) LIPOPOLYS	Hs.204238	0.99	0.77	-	-	0.89	0.68
LCK: (LCK)PROTO-ON	Hs.2488	0.52	0.41	-	4.72	0.65	0.84
LCN2: (LCN2 OR NGAL	Hs.44865	0.57	-	0.83	-	1.46	1.16
LCP2: (LCP2) LYMPHOC	Hs.25195 Hs.278239	0.78	1.70	-	2.43	1.18	2.69
LEF1: (LEF1) LYMPHOI	Hs.411701	1.83	0.75	0.67	0.98	1.28	1.34
LEFTA-LEFTB_HUMAN: (	Hs.2250	0.99	1.41	-	1.19	1.47	1.35
LGALS3: (LGALS3 OR M	Hs.446501	0.54	1.25	-	1.90	1.44	0.92
LIF: (LIF OR HILDA)	Hs.100299	1.55	0.51	-	1.37	1.39	1.17
LIFRA: (LIFR) LEUKEM	Hs.166091	0.92	1.23	-	-	-	1.68
LIG3: (LIG3) DNA LIG	Hs.2799	1.23	-	-	0.86	0.93	0.93
LIG4: (LIG4) DNA LIG	Hs.76507	-	-	-	1.45	-	1.42
LINK: (CRTL1) PROTEO	Hs.81118	1.17	-	-	1.14	1.30	1.23
LITAF: (LITAF OR PIG	Hs.3844	1.48	0.77	-	1.66	0.64	0.85
LKHA: (LTA4H OR LTA4	Hs.148830	0.71	1.20	-	1.32	1.78	1.27
LMO4: (LMO4) LIM DOM	Hs.162757	0.90	0.75	1.20	0.60	0.95	1.22
LRAT: (LRAT) LECITHI	Hs.56729	0.78	0.72	-	0.94	1.47	0.91
LRP1: (LRP1 OR A2MR)	Hs.241257	1.98	0.86	-	1.81	0.98	1.38
LSP1: (LSP1 OR WP34	Hs.105689	1.11	0.58	-	1.53	-	0.95
LTBP1: (LTBP1) LATEN	Hs.289019	0.87	-	-	-	0.74	0.97
LTBP2: (LTBP2) LATEN	Hs.85087	1.17	-	-	1.34	0.95	1.25
LTBP3: (LTBP-3) LATE	Hs.1116	0.55	1.63	-	-	0.87	1.58
LTBP4: LATENT TRANSF	Hs.287921	1.25	-	-	-	0.88	1.18
LTBR: (LTBR OR TNFCR	Hs.406475	2.74	-	-	0.35	1.60	0.68
LUMAN: (CREB3 OR LZI	Hs.153563	1.65	-	-	0.57	0.87	0.64
LUMICAN: (LDC) LUMIC	Hs.80887	0.44	0.53	0.59	1.68	0.28	0.76
LY75: (LY75) RECEPTO	Hs.87860	1.13	0.54	-	-	1.14	1.65
LYN: (LYN) TYROSINE-	Hs.102267	1.14	-	-	1.38	0.98	0.95
LYP1: (PTPN8) HEMATO	Hs.102598	0.74	0.60	0.50	1.56	1.39	0.93
LYSYLOXIDASE: (LOX)	Hs.82548	5.33	0.59	-	-	0.78	1.38
MADCAM-1: (MADCAM-1)	Hs.169487	0.91	-	-	1.75	0.83	0.90
MADD: (MADD) MAP KIN	-	0.99	-	0.47	-	1.00	1.25
MAF1: (MAFB) MAFB/KR	-	1.26	1.25	-	1.56	1.24	1.66
MAFF: (MAFF OR BK447	Hs.134859	1.11	0.87	0.89	0.69	0.96	0.84
MAFG: (MAF OR MAFG)	Hs.389137	1.15	0.63	0.33	0.60	1.17	-
MAF-SHORT: (MAF OR M	Hs.300946	1.43	-	-	1.17	1.92	0.82
MAGP1: (MFAP2 OR MAG	Hs.132311	1.84	0.83	-	1.67	0.54	-
MAGP2: (MFAP5 OR MAG	Hs.366546	-	1.10	-	5.81	-	0.95
MAP: MAP KINASE PHOS	Hs.180533	0.84	-	-	0.64	1.38	0.84
MAP2K1: (MAP2K1 OR P	Hs.436145	0.88	-	-	0.52	0.93	1.85
MAP2K2: (MAP2K2 OR P	Hs.256924	2.27	0.57	-	0.45	1.19	0.78
MAP2K3: (MAP2K3 OR P	Hs.110299	0.88	0.96	-	0.41	0.68	0.62

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MAP2K5: (MAP2K5 OR P	Hs.28827	-	-	-	1.56	-	0.85
MAP2K6: (MAP2K6 OR P	Hs.390428	-	-	-	1.14	1.23	0.97
MAP2K7: (MAP2K7 OR P	Hs.290346	1.88	-	-	1.27	1.60	0.98
MAP3K2: (MAP3K2 OR M	Hs.432453	1.42	1.26	-	1.40	1.25	1.43
MAP3K4: (MAP3K4 OR M	Hs.324473	1.00	-	-	1.16	1.16	0.98
MAP3K7: (MAP3K7 OR T	Hs.25209	1.45	-	-	1.40	0.90	1.79
MAP3K8: (MAP3K8 OR C	Hs.57732	1.14	0.43	-	1.27	1.15	1.47
MAPK1: (MAPK1 OR P	Hs.79107	0.56	1.17	-	0.49	0.73	0.88
MAPK1: (MAPK1 OR PRK	Hs.861	1.16	-	-	1.92	0.99	1.46
MAPK11: (MAPK11 OR P	Hs.433728	0.96	0.79	0.52	1.66	1.92	1.43
MAPK14: (MAPK14 OR C	Hs.271980	1.15	-	-	1.69	-	1.17
MAPK3: (MAPK3 OR PRK	Hs.150136	0.97	0.92	0.85	0.75	1.24	0.98
MAPK4: (MAPK4 OR PRK	Hs.445864	1.34	1.24	0.63	1.15	1.44	0.87
MAPK6: (MAPK6 OR PRK	Hs.234249	1.17	-	-	-	-	-
MAPK7: (MAPK7 OR PRK	Hs.356523	0.84	-	-	-	-	1.34
MAPK8: (MAPK8 OR PRK	Hs.348446	1.49	0.48	-	1.30	1.16	1.29
MAPK8IP1: (MAPK8IP1	Hs.75074	1.41	-	-	1.90	1.20	0.95
MAPK8IP2: (MAPK8IP2	Hs.413901	1.51	1.88	-	1.23	-	1.27
MAPK9: (MAPK9 OR PRK	Hs.437808	0.91	-	-	1.19	0.84	0.94
MAPKAPK2: (MAPKAPK2	Hs.150366	1.23	-	-	0.27	0.64	0.66
MAPKAPK5: (MAPKAPK5)	Hs.153647	0.72	1.43	-	0.41	1.15	1.90
MATK: (MATK OR CTK O	Hs.278461	0.63	-	-	1.77	0.97	0.98
MATRILIN1: (MATN1 OR	Hs.223745	-	-	-	-	-	0.92
MATRILIN2: (MATN2) M	Hs.365706	1.45	1.38	-	-	0.17	0.55
MATRILIN3: (MATN3) M	Hs.511397	1.21	0.63	-	0.46	1.25	0.88
MATRIN3: (MATR3) MAT	Hs.86386	0.55	0.89	-	0.27	0.83	1.19
MATRIXGLA: (MGP) MAT	Hs.83532	0.28	-	-	0.56	0.14	0.65
MCAM: (MCAM OR MUC18	Hs.2442	-	-	-	1.85	0.58	1.44
MCL1: (MCL1) INDUCED	Hs.79748	1.52	-	-	0.86	0.74	1.41
MCP: (MCP) MEMBRANE	Hs.55173	0.42	-	-	1.45	0.34	1.29
MDC9: (ADAM9 OR MDC9	Hs.389700	5.66	-	-	2.52	0.76	1.71
MDU1: (SLC3A2 OR MDU	Hs.81874	0.35	0.16	0.27	0.11	1.66	0.16
MEGF2: (MEGF2) MEGF2	Hs.212507	-	-	-	-	0.89	0.88
MGST1: (MGST1 OR MGS	Hs.283477	0.62	0.87	-	0.18	1.30	0.82
MGST2: (MGST2 OR GST	Hs.12256	0.32	-	-	0.18	1.72	0.45
MGST3: (MGST3) MICRO	Hs.89690	0.60	0.96	-	0.39	1.45	1.64
MIC2_HUMAN: ((CD99X	-	1.19	0.75	-	1.96	1.26	0.99
MID2: (MID2 OR FXY2)	Hs.54403	0.64	-	-	-	-	1.42
MIG-2: MIG-2 PROTEIN	Hs.100469 Hs.280306	0.76	-	-	-	0.78	0.96
MIP2B_HUMAN: (CXCL3	Hs.79889	0.82	-	-	-	-	1.13
MMD: (MMD) MONOCYTE	Hs.83169	1.30	-	-	1.62	1.36	-
MME: (MME OR EPN) NE	Hs.2258	1.26	1.54	-	0.23	1.39	1.76
MMP1: (MMP1 OR STM	Hs.143751	-	0.55	-	-	-	0.44
MMP11: (MMP11 OR STM	Hs.2936	-	-	-	-	-	1.00
MMP12: (MMP12 OR HME	Hs.2399	2.19	-	-	1.77	-	1.37
MMP13: (MMP13) COLLA	Hs.80343	-	0.68	-	-	-	1.16
MMP14: (MMP14 OR MMP	Hs.90800	1.12	-	-	1.55	0.92	1.23
MMP15: (MMP15) MATRI	Hs.159581	1.56	1.12	0.44	0.82	1.16	1.27
MMP16: (MMP16 OR MMP	Hs.154057	1.35	0.89	-	1.49	1.70	1.52
MMP17: (MMP17 OR MT4	Hs.367877	1.14	0.94	-	1.45	1.23	0.96
MMP18: (MMP19 OR MMP	Hs.123387	1.35	-	-	3.15	-	1.37
MMP2: (MMP2 OR CLG4A	Hs.211819	3.46	-	-	0.68	0.72	1.21
MMP2: (MMP2) MATRI	Hs.212581	0.86	-	-	-	0.96	1.18
MMP21-22-23: (MMP-23	Hs.528670	1.33	-	-	1.16	0.99	0.81
MMP24: (MMP24 OR MT5	Hs.380710	1.22	-	-	1.93	0.99	0.92
MMP25: (MMP25 OR MT6	Hs.375129	0.96	1.18	-	-	1.75	1.15
MMP28: (MMP28) MATRI	Hs.2256	1.20	1.53	-	-	0.95	-
MMP3: (MMP3 OR STMY1	Hs.390002	-	0.68	-	-	-	0.88
MMP7: (MMP7 OR MPSL1	Hs.151738	0.15	-	-	0.46	3.81	1.80
MMP8: (MMP8 OR CLG1)	Hs.511804	0.99	-	-	1.58	1.80	1.86
MMP9: (MMP9 OR CLG4B	Hs.184601	-	-	-	-	-	1.27
MOB-LAK: (MOB-LAK OR	Hs.422215	1.74	-	-	0.98	1.15	1.35
MPE16: (SLC7A5 OR LA	Hs.75182	1.12	-	-	1.41	1.27	0.84
MPP1: (MPP1 OR EMP55	Hs.438040	0.77	0.99	0.57	0.49	1.57	0.89
MRC1: (MRC1) MACROPH	Hs.432458	1.17	0.39	-	1.81	-	0.58
MS4A1: (MS4A1 OR CD2	Hs.2942	-	-	-	-	-	1.11
MSF: (PRG4) MEGAKARY	Hs.407830	1.26	0.86	-	1.25	1.42	-
MST1R: (MST1R OR RON	Hs.82116	1.29	2.00	-	1.26	1.45	1.17
MYB: (MYB) MYB PROTO	Hs.25812	1.65	0.88	0.67	0.43	0.98	0.98
MYD88: (MYD88) MYELO	Hs.78792	0.83	0.60	0.92	-	0.64	0.74
NAP4: (SOCS6 OR NAP4	Hs.1565	-	-	-	-	-	0.87
NBS1: (NBS1 OR NBS)	Hs.99863	0.89	-	-	-	-	1.15
NCAM1_3: (NCAM1 OR N	Hs.356321	1.22	-	-	1.57	1.42	1.18
NED4: (NEDD4 OR KIAA	Hs.77810	1.26	1.00	-	0.71	0.88	1.00
NELASTASE: (ELA2) LE	Hs.512591	1.29	-	-	0.54	1.23	0.84
NFAT1: (NFATC2 OR NF	Hs.172674	0.82	1.20	-	1.51	0.87	1.15
NFAT3: (NFATC4 OR NF	Hs.75643	1.31	-	-	1.19	1.12	1.58
NFATCB: (NFATC1 OR N	Hs.83469	1.29	-	-	1.19	1.34	0.98
NFATX: (NFATC3 OR NF	Hs.160557	0.79	0.78	-	0.75	0.84	0.97
NF-E2: (NFE2) TRANSC	Hs.73090	0.92	0.78	-	1.69	0.93	0.89
NFE2L1: (NFE2L1 OR N	Hs.132594	0.89	0.56	-	0.75	0.87	0.78
NFKB1: (NFKB1) NUCLE	Hs.356764	0.72	-	-	0.84	0.98	0.97

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NFKB2: (NFKB2) NUCLE	Hs.413074	1.13	0.83	-	0.62	1.22	0.82
NFKB3: (RELA OR NFKB	Hs.356624	1.23	0.72	-	0.77	0.92	0.80
NFX1: (NFX1) TRANSCR	Hs.135201	0.88	-	-	-	0.96	0.86
NIDOGEN: (NID) NIDOG	Hs.193788	1.50	-	-	1.91	1.19	0.96
NOD2: (CARD15 OR NOD	Hs.311559	0.87	1.18	-	-	0.97	1.15
NOTCH1: (NOTCH1 OR T	Hs.8121	1.23	-	-	0.67	1.25	1.12
NOTCH2: (NOTCH2) NEU	Hs.436100	1.41	1.29	-	1.36	1.44	-
NOTCH4: (NOTCH4) NOT	Hs.155396	0.79	-	-	0.75	1.38	0.96
NRF2: (NFE2L2 OR NRF	Hs.173548	0.32	-	-	0.56	1.12	1.34
NRP1: (NRP1 OR NRP O	Hs.151123	1.50	0.49	0.62	1.64	1.49	1.37
NSHC: (SHC3) P64 ISO	Hs.153952	0.96	0.70	0.43	-	-	1.26
NT5: (NT5E OR NT5 OR	Hs.511760	1.23	2.87	-	1.13	1.48	1.16
NTE: NTE NEUROPATHY	Hs.332115	1.25	-	-	1.57	1.35	1.16
NUMA: NUMA PROTEIN.	Hs.241385	0.83	0.90	-	-	0.79	1.30
OP4: (OPHN4) OLIGOPH	Hs.313	1.29	-	-	0.51	1.00	1.14
OPN: (SPP1 OR OPN) O	Hs.278388	0.79	-	-	1.18	5.65	1.63
ORM1: (ORM1 OR AGP1)	Hs.277704	0.84	-	-	0.65	0.86	0.85
ORP15: (HYOU1 OR OR	Hs.47011	1.39	1.82	1.15	0.64	1.21	2.23
OSF: (OSTF1 OR SH3D3	Hs.135554	1.12	-	-	2.58	1.30	0.74
OSP94: (OSP94) OSMOT	Hs.512679	1.17	0.64	-	1.64	1.48	0.96
OSTEOCALCIN: (BGLAP)	Hs.278186	-	1.29	-	0.56	-	1.59
P115RHOGEF: (ARHGEF1	Hs.408312	-	1.35	-	-	-	0.95
P53: (TP53 OR P53) C	Hs.512592	-	-	-	-	-	0.78
P53R2: (P53R2) RIBON	Hs.192132	1.23	-	-	1.48	-	1.32
P73_1: (TP73 OR P73)	Hs.992	1.34	-	-	1.45	1.22	1.21
PA21: (PLA2G1B OR PL	Hs.93304	1.18	-	-	1.29	0.97	1.19
PAFA: (PLA2G7) PLATE	Hs.77318	1.70	-	-	3.60	1.15	1.12
PAFAH1B1: (PAFAH1B1	Hs.414795	0.66	0.75	-	0.49	1.85	1.28
PAI1: (SERPINE1 OR P	Hs.75716	15.53	0.80	-	5.39	-	1.12
PAI2: (SERPINB2 OR P	Hs.154299	1.28	-	-	1.18	1.36	1.25
PAR2: (PAR2 OR GPR11	Hs.42502	0.55	0.99	-	0.59	0.53	1.37
PAR3: (F2RL2 OR PAR3	Hs.406074	0.60	-	-	1.17	-	0.94
PAR-4: PROSTATE APOP	Hs.430919	1.23	-	-	0.68	1.85	0.93
PC3B: (BTG4 OR PC3B)	Hs.128180	0.96	-	-	1.27	1.17	0.57
PCNA: (PCNA) PROLIFE	Hs.78996	0.66	-	-	0.35	1.16	1.38
PCTK2: (PCTK2) SERIN	Hs.258536	0.76	0.85	-	0.94	0.60	1.85
PDGA: (PDGFA OR RPA1	Hs.376032 Hs.521331	-	-	-	1.33	-	0.72
PDGB: (PDGFB OR C-SI	Hs.1976	1.18	0.62	-	1.12	0.76	0.88
PDGFRA: (PDGFRA) ALP	Hs.74615	0.93	-	-	1.40	1.62	1.23
PDGFRB: (PDGFRB OR P	Hs.307783	1.18	-	-	1.55	1.23	1.42
PD-L2: (PDL2) BUTYRO	Hs.61929	1.77	-	-	0.61	0.89	1.14
PECAM1: (PECAM1 OR P	Hs.78146	0.56	1.13	-	2.59	0.42	1.76
PGH2: (PTGS2 OR COX2	Hs.196384	1.28	1.13	0.78	0.85	1.17	0.96
PGS2: (DCN) BONE PRO	Hs.83974	0.38	1.42	-	0.34	0.32	0.64
PGT: (SLC21A2) PROST	Hs.75251	0.80	0.90	0.68	0.51	1.24	0.88
PIAS1: (PIAS1 OR DDX	Hs.441069	0.76	0.39	2.25	0.96	0.68	0.66
PIAS3: (PIAS3) PROTE	Hs.435761	0.82	0.55	-	0.78	0.75	0.77
PIASG: (PIASG) PROTE	Hs.105779	-	-	-	1.64	-	0.94
PIASX: (PIASX OR PIA	Hs.249235	0.96	-	-	1.10	-	0.92
PIK3C2A: (CPK-M OR P	Hs.22500	-	-	-	1.50	-	1.26
PIK3C2G: (PIK3C2G) P	Hs.85701	-	0.00	-	-	-	1.16
PIK3CA: (PIK3CA) P11	Hs.239818	1.39	0.81	-	1.37	1.33	1.39
PIK3CB: (PIK3CB) PHO	Hs.426967	0.85	-	-	-	0.69	0.85
PIK3CD: (PIK3CD) PHO	Hs.32942	1.14	0.75	-	1.64	-	1.49
PIK3CG: (PIK3CG) PHO	Hs.6241	-	-	-	-	-	0.94
PIK3R1: (PIK3R1 OR G	Hs.372548	0.83	-	-	0.98	1.00	1.14
PIK3R3: (PIK3R3) PHO	Hs.81170	0.96	-	-	-	-	-
PIM1: (PIM1) PROTO-O	Hs.18586	1.32	-	-	0.78	1.16	1.94
PK428: (MRCK) MYTONI	Hs.155342	0.98	-	-	0.84	-	0.98
PKCD: (PRKCD OR PKCD	Hs.211587	1.89	0.82	-	0.51	-	0.97
PLA2G4: (PLA2G4A OR	Hs.149623	0.79	-	-	1.62	0.85	0.43
PLA2-III: (PLA2G3 OR	Hs.179657	-	-	-	1.58	-	1.23
PLAUR: (PLAUR OR UPA	Hs.429643	1.56	-	-	2.12	1.46	1.15
PLC: (PLC-L) PHOSPHO	Hs.355888	-	0.84	-	-	0.77	1.26
PLCB1: (PLCB1) 1-PHO	Hs.437137	1.17	-	-	1.17	1.82	1.20
PLCB2: (PLCB2) 1-PHO	Hs.151408	-	-	-	1.98	-	0.79
PLCB3: (PLCB3) 1-PHO	Hs.380094	-	-	-	1.31	-	0.90
PLCB4: (PLCB4) PHOSP	Hs.80776	-	-	-	1.69	-	1.15
PLC-BC1668: (PLC-B	Hs.103417	1.29	-	-	1.25	0.97	1.32
PLCD1: (PLCD1) 1-PHO	Hs.268177	0.93	-	-	-	0.98	0.99
PLCE: (PLCE OR PLCE1	Hs.512298	1.15	-	-	0.62	-	1.23
PLCG1: (PLCG1 OR PLC	Hs.153322	0.33	-	-	0.46	0.73	1.13
PLCG2: (PLCG2) 1-PHO	Hs.270411	-	-	-	0.19	0.50	0.85
PLGF: (PGF OR PLGF)	Hs.252820	1.35	1.12	-	0.93	1.17	0.63
PNP: (ADAMTS2 OR PCI	Hs.444234	1.41	-	-	1.42	1.36	0.32
POU2F1: (POU2F1 OR O	Hs.271640	0.91	1.24	-	0.55	1.35	0.92
PPAR: (PPARA OR NR1C	Hs.177766	1.99	0.85	-	0.44	1.90	1.12
PPOL: (ADPRT OR PPOL	Hs.76494	-	0.65	-	0.79	0.83	0.76
PRELP: (PRELP) PROLA	Hs.2200	1.93	-	-	1.52	0.83	0.81
PRF1: (PRF1) PERFORI	Hs.69171	-	-	-	-	-	0.87
PRK2: (PRKCL2 OR PRK	Hs.349611	0.86	-	-	-	0.86	1.90
PRKCA: (PRKCA OR PKC	Hs.349845	-	-	-	-	-	1.46

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PRKCB_2: (PRKCB OR P	Hs.349845	0.59	0.58	-	3.11	-	0.82
PRKCB_3: (PRKCB OR P	Hs.349845	0.67	-	-	1.64	0.81	0.93
PRKCB_4: (PRKCB OR P	Hs.155281	0.62	-	-	1.82	0.57	-
PRKCE: (PRKCE OR PKC	Hs.315366	0.92	-	-	1.23	0.82	-
PRKCH: (PRKCH OR PKC	Hs.407181	0.79	-	-	1.19	0.74	-
PRKCZ: (PRKCZ OR PKC	Hs.1905	-	-	-	-	-	1.33
PRL_1: (PRL) PROLACT	Hs.212892	1.28	0.89	-	0.96	1.31	0.92
PRLR: (PRLR) PROLACT	Hs.82353	1.11	-	-	0.53	1.14	0.85
PROCR: (PROCR OR EPC	Hs.75111	1.42	-	-	1.26	-	1.23
PRSS11: (PRSS11 OR H	Hs.46	0.90	0.81	-	0.30	1.44	0.86
PTAFR: (PTAFR OR PAF	Hs.159526	0.99	-	-	3.42	1.20	0.94
PTCH: (PTCH) PATCHED	Hs.249164	1.26	-	-	1.50	1.24	0.90
PTCH2: (PTCH2) PATCH	Hs.253309 Hs.493716	0.95	-	-	-	1.28	0.54
PTEN1-PTEN2: (PTEN O	Hs.306831	0.68	-	-	0.54	0.91	1.43
PTGDR: (PTGDR) PROST	Hs.2090	1.28	-	-	1.37	1.32	0.82
PTGER2: (PTGER2) PRO	Hs.89418	1.13	-	-	1.85	1.29	0.91
PTGFR: (PTGFR) PROST	Hs.458324	0.79	1.13	0.66	-	0.76	0.94
PTGIR: (PTGIR OR PRI	Hs.387553	-	0.86	-	1.12	-	0.96
PTP: (PTPN13 OR PTP1	Hs.83572	0.38	-	-	0.39	0.96	-
PTP2C: (SHPTP2 OR PT	Hs.43666	-	-	-	-	-	1.60
PTP4A3: (PTP4A3 OR P	Hs.446126	-	0.56	-	1.53	0.98	1.82
PTPL1-AR: PTPL1-ASSO	Hs.63489	0.98	-	-	1.35	0.79	0.83
PTPN2: (PTPN2 OR PTP	Hs.63489	0.61	0.73	0.41	1.29	1.62	1.39
PTPN6_1: (PTPN6 OR P	Hs.402773	0.73	-	-	1.72	1.25	1.47
PTPN6_2: (PTPN6 OR P	Hs.75216	-	-	-	1.78	-	1.83
PTPN7: (PTPN7) PROTE	Hs.171992	1.25	0.62	-	1.95	-	1.34
PTPRF: (PTPRF OR LAR	Hs.76452	1.25	-	-	-	-	1.11
PTPRJ: (PTPRJ OR DEP	Hs.171844	0.85	-	-	-	0.83	1.12
PTX1: (PTX1 OR CRP)	Hs.405474	1.79	-	-	0.93	0.94	0.86
PVS_1_HUMAN: (PVS OR	Hs.73958	1.27	1.16	-	1.23	1.28	1.92
PYK2: (PTK2B OR FAK2	Hs.159376	1.23	0.82	0.72	1.11	-	0.85
RAG1: (RAG1) V(D)J R	Hs.324051	1.34	-	-	1.33	1.35	0.94
RAG2: (RAG2) V(D)J R	Hs.302498	0.93	0.81	-	0.93	0.98	0.95
RAI: (RAI) RELA ASSO	Hs.758	3.78	1.28	-	0.74	1.26	1.32
RAR: (RAB4B OR SEC4	Hs.307905	0.41	-	-	-	1.94	0.89
RASA1_2: (RASA1 OR R	Hs.75256	-	-	-	1.90	-	-
RELB: (RELB) TRANSCR	Hs.77273	1.26	-	-	1.31	1.85	0.73
RGS1: (RGS1 OR 1R2	Hs.406064	0.69	-	-	11.33	0.98	1.42
RHOA: (ARHA OR ARH12	Hs.16986	0.94	-	-	0.53	0.99	0.94
RHOB: (ARHB OR ARH6	Hs.282386	1.11	-	-	0.52	0.88	1.47
RHOD-AK198: (RHOD	Hs.33254	1.14	0.35	-	0.73	1.38	0.98
RHOD-AL359617: (TSGA	Hs.430725	1.97	1.95	-	0.84	1.56	0.85
RHOIP2: (RHOIP2) RHO	Hs.390758	1.18	0.68	-	0.74	1.13	0.88
RHOIP3: (RHOIP3) RHO	Hs.75447	0.38	-	-	0.41	0.67	0.98
RIPK1: (RIPK1 OR RIP	Hs.9238	1.49	1.40	-	1.25	1.52	0.98
RLIP76: (RIP1) RLIP7	Hs.435065	0.84	1.17	-	-	0.76	0.57
RNF3A: (RNF3A) RING	Hs.444012	1.17	1.98	-	0.82	1.16	0.97
RPS7: (RPS7) 4S RIB	Hs.9651	0.78	-	-	0.40	0.51	0.99
RRAS: (RRAS) RAS-REL	Hs.206097	2.20	0.31	0.50	0.69	1.16	0.75
RRAS2: (RRAS2) RAS-R	Hs.252189	2.15	-	-	0.90	1.77	0.94
RYUDOCAN: (SDC4) SYN	Hs.19413	1.63	-	-	-	-	1.29
S1A12_HUMAN: (S1	Hs.512813	1.25	1.16	0.71	1.43	1.38	0.76
SALT	Hs.380906	-	-	-	-	-	1.28
SAP3: (SAP3) SIN3-	Hs.458346 Hs.174228	0.84	0.78	0.67	1.20	1.90	0.99
SARP1: (SARP1) SECRE	Hs.89546	1.20	1.28	-	0.95	0.88	-
SARP2: (SARP2)SECR	Hs.78979	1.26	-	-	0.62	2.23	1.15
SB135: (MYADM OR MUG	Hs.82848	1.30	0.67	-	-	0.94	0.96
SCYC1-SCYC2: (SCYC1	Hs.423077	3.58	1.29	-	2.72	1.67	0.88
SELE: (SELE OR ELAM1	Hs.511748	-	-	-	-	-	1.74
SELEL: (SELEL OR ESL	Hs.24640	1.22	0.57	0.27	0.55	1.46	6.92
SELL: (SELL OR LYAM1	Hs.278311	0.95	-	-	1.98	1.23	0.98
SELPLG: (SELPLG) P-S	Hs.297681	-	1.40	-	3.49	-	0.82
SEMA4D: (SEMA4D OR C	Hs.381167	1.62	1.23	-	1.45	1.25	1.23
SEMAL: (SEMA7A OR SE	Hs.241579	1.13	-	-	1.13	1.16	1.81
SEP: (SEP OR PLEXIN-	Hs.41691	1.79	1.15	-	-	-	1.12
SERPINA1_1_HUMAN: (S	Hs.7306	0.49	0.41	-	0.39	4.50	1.92
SERPINB1: (SERPINB1	Hs.31386	0.57	-	-	0.95	1.34	1.66
SERPINH1-SERPINH2: (	Hs.433795	3.54	1.49	-	0.76	0.92	0.87
SFA2: (BATF) ATF-LIK	Hs.262886	1.24	-	-	1.25	1.28	2.80
SHC1: (SHC1 OR SHC)	Hs.440896	1.49	-	-	2.32	0.88	1.25
SHIP: (INPP5D OR SHI	Hs.99724	1.83	0.69	0.54	1.26	0.98	0.93
SIP1_1: (SLC9A3R2 OR	Hs.89864	1.18	-	-	-	0.68	1.37
SKAT2: (SKAT2) ZINC	Hs.23348	0.98	1.52	-	0.83	1.23	1.00
SKIV2L: (SKIV2L OR S	Hs.32970	1.15	-	-	0.71	1.12	0.39
SKP2: (SKP2) CYCLIN	Hs.169611	-	0.97	-	-	-	1.12
SLAM: (SLAM) SIGNALI	Hs.388294	0.60	0.75	-	2.31	-	0.93
SMAC: (6141G12RIK	Hs.110741	0.89	-	-	-	0.86	1.28
SMAD1: (MADH1 OR SMA	Hs.167700	0.86	-	-	1.00	0.97	1.15
SMAD2: (MADH2 OR SMA	Hs.123119	0.82	-	-	0.72	1.53	0.65
SMAD5: (MADH5 OR SMA	Hs.50640	1.85	0.59	-	1.83	1.25	1.16
SMAD9: (MADH9 OR SMA	Hs.405946	1.13	0.85	-	1.22	1.39	1.29
SOCS1: (SOCS-1 OR SS	Hs.436943	0.78	0.78	0.51	0.65	0.97	0.94

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SOCS2: (HSSOCS-2) SU	Hs.169836	1.28	0.76	0.55	1.75	1.25	0.93
SOCS3: (SOCS3) STAT	Hs.44439	-	0.56	-	1.45	1.13	0.74
SOD1: (SOD1) SUPEROX	Hs.270564	0.32	0.90	0.88	0.12	1.30	0.98
SOD2: (SOD2 OR SOD-2	Hs.443914	1.84	-	-	3.80	1.18	1.86
SODD: (BAG4 OR SODD)	Hs.384944	0.97	0.37	0.29	1.55	0.87	0.47
SOS1: (SOS1) SON OF	Hs.194726	0.98	0.89	-	1.67	0.73	1.20
SOS2: (SOS2) SON OF	Hs.326392	0.68	-	-	1.35	1.37	1.80
SP1: (SP1) TRANSCRIP	Hs.528126	1.21	-	-	1.18	1.29	1.12
SP3: (SP3) TRANSCRIP	Hs.9460	1.75	0.63	0.55	0.83	1.27	1.31
SPA2L2: (PLA2-XIII O	Hs.154295	-	1.15	-	-	-	0.92
SPARC: (SPARC OR ON)	Hs.333175	3.47	0.98	-	1.12	0.46	0.94
SPLASH: (PLA2G2D OR	Hs.111779	1.35	1.61	-	1.52	1.22	0.42
SPN: (SPN OR CD43) L	Hs.189507	-	0.31	-	-	-	1.12
SPOCK: (TESTICAN) TE	Hs.461934	1.17	-	-	1.92	1.18	1.14
SPRY1: (SPRY1) SPROU	Hs.93029	0.43	1.35	-	0.55	0.96	1.12
SRC: (SRC OR SRC1) P	Hs.436944	1.27	1.58	-	0.95	-	0.93
SRCAP: (SRCAP) TRANS	Hs.436015	0.82	-	-	-	1.13	0.86
SRE1_1: (SREBF1 OR S	Hs.136227	1.84	-	-	1.44	1.78	0.96
SRF: (SRF) SERUM RES	Hs.426528	-	-	-	-	-	1.96
ST2L: (ST2) ST2L (LY	Hs.444086	1.20	-	-	1.20	1.32	1.94
STAT1: (STAT1) SIGNA	Hs.21486	1.32	-	-	3.32	1.18	1.16
STAT2: (STAT2) SIGNA	Hs.72988	1.28	1.50	-	1.52	1.15	1.76
STAT3: (STAT3 OR APR	Hs.421342	1.44	-	-	0.43	0.70	0.97
STAT4: (STAT4) SIGNA	Hs.80642	0.98	0.64	0.73	2.76	-	0.65
STAT5A: (STAT5A OR S	Hs.437058	1.12	-	-	0.98	0.97	1.37
STAT5B: (STAT5B) SIG	Hs.434992	1.44	-	-	1.38	1.43	0.93
STAT6: (STAT6) SIGNA	Hs.437475	0.94	0.94	-	0.97	0.98	1.18
STCH: (STCH) MICROSO	Hs.352341	1.16	-	-	-	1.40	1.25
STX3A_2: (STX3A OR S	Hs.82240	0.92	1.20	-	-	0.85	0.96
SYK: (SYK) TYROSINE-	Hs.192182	-	-	-	1.27	-	0.87
SYNDECAN1: (SDC1 OR	Hs.82109	1.16	-	-	2.82	0.82	0.95
SYNDECAN2: (SDC2 OR	Hs.1501	0.57	-	-	0.69	0.92	0.93
SYNDECAN3: (SDC3 OR	Hs.158287	-	-	-	-	-	1.23
TACE: (ADAM17 OR TAC	Hs.404914	1.12	-	-	0.66	1.00	0.96
TACI: (TNFRSF13B OR	Hs.158341	0.97	0.69	-	1.73	1.14	0.83
TANK: (TANK OR ITRAF	Hs.146847	0.56	-	-	1.45	0.67	1.63
TBLYM_BAD: (TBX21 OR	Hs.272409	0.79	-	-	0.90	1.31	1.43
TCF12: (TCF12 OR HTF	Hs.438166	1.57	-	-	1.40	0.97	1.39
TCF3: (TCF3 OR E2A O	Hs.371282	1.30	1.25	-	1.32	1.16	1.17
TCF4: (TCF4 OR ITF2	Hs.359289	0.78	0.84	0.62	1.35	0.79	0.88
TDGF1-TDGF3_2_HUMAN:	Hs.496585 Hs.385870	1.25	-	-	1.13	1.34	0.74
TDT: (DNTT OR TDT) D	Hs.397294	1.37	1.43	0.74	1.35	1.29	1.50
TEF: (TEF) THYROTROP	Hs.181159	1.35	1.37	-	1.96	1.28	0.94
TENASCINR: TENASCIN-	Hs.54433	1.32	1.29	-	1.82	1.63	0.90
TFE3: (TFE3) TRANSCR	Hs.274184	0.83	-	-	-	0.86	1.44
TFRC_MIDDLE: (TFRC)	Hs.185726	-	-	-	2.41	0.88	1.27
TGFA55: (TGFA) TRANS	Hs.170009	-	0.65	0.32	1.36	-	1.23
TGFB1_1: (TGFB1 OR T	Hs.1103	1.33	-	-	1.29	0.96	1.10
TGFB2: (TGFB2) TRANS	Hs.169300	0.99	-	-	1.15	1.28	0.42
TGFB3_1: (TGFB3 OR T	Hs.2025	1.16	-	-	1.24	1.25	1.32
TGFBI: (TGFBI OR BIG	Hs.421496	17.40	1.45	-	6.65	0.52	1.00
TGFBR1: (TGFBR1) TGF	Hs.28005	0.89	-	-	0.95	0.91	1.98
TGFBR2: (TGFBR2) TGF	Hs.82028	1.29	-	-	2.59	-	0.82
THBD: (THBD OR THRM)	Hs.2030	-	-	-	-	-	1.32
THROMBOSPONDIN1: (TH	Hs.164226	1.21	-	-	1.12	1.24	-
THROMBOSPONDIN2: (TH	Hs.458354	16.94	0.88	-	5.68	-	0.92
THROMBOSPONDIN3: (TH	Hs.169875	1.53	-	-	1.36	1.39	1.86
THROMBOSPONDIN4: (TH	Hs.415041	1.62	-	-	1.85	1.30	1.13
THROMBOSPONDIN5: (CO	Hs.134643	0.49	1.15	-	1.78	0.64	0.97
THY1: (THY1) THY-1 M	Hs.115176	1.33	-	-	0.83	1.36	0.84
TIAM: (TIAM) T-LYMPH	Hs.446641	1.10	0.52	-	-	-	0.82
TIMP1: (TIMP1 OR TIM	Hs.6441	1.50	-	-	7.14	1.95	1.52
TIMP2: (TIMP2) METAL	Hs.245188	2.29	1.54	-	2.73	1.70	4.17
TIMP3: (TIMP3) METAL	Hs.190787	1.23	1.88	-	0.57	0.68	1.55
TIMP4: (TIMP4) METAL	Hs.17681	1.37	-	-	1.25	1.33	0.78
TIRAP: (TIRAP OR MAL	Hs.89643	0.82	1.23	-	-	0.97	0.88
TKT: (DDR2 OR NTRKR3	Hs.111805	0.88	-	-	1.54	-	1.51
TKT1: (TKT1 OR TKT)	Hs.120551	1.19	-	-	0.73	0.79	0.87
TLR1: (TLR1 OR KIAA	Hs.519033	1.86	-	-	0.60	1.26	0.92
TLR1_HUMAN: (TLR1)	Hs.29499	1.28	-	-	1.25	1.33	1.36
TLR2: (TLR2 OR TIL4)	Hs.174312	1.13	0.56	-	2.17	1.38	0.98
TLR3: (TLR3) TOLL-LI	Hs.114408	0.68	-	-	1.30	0.89	1.17
TLR4: (TLR4)TOLL-L	Hs.366986	1.37	-	-	1.45	1.38	1.39
TLR5: (TLR5 OR TIL3)	Hs.179152	1.12	0.74	0.53	0.59	0.98	0.88
TLR6: (TLR6) TOLL-LI	Hs.87968	1.15	0.66	-	0.64	1.75	0.88
TLR7: (TLR7) TOLL-LI	Hs.351316	1.29	-	-	1.30	1.55	0.81
TLR9: (TLR9) TOLL-LI	Hs.439586	1.32	0.98	0.62	0.94	1.11	0.95
TM4SF1: (TM4SF1 OR T	Hs.98998	1.00	-	-	0.53	0.76	0.92
TM4SF2: (TM4SF2 OR M	Hs.241570	0.45	0.57	0.42	0.39	0.58	0.92
TNC: (TNC OR HXB) TE	Hs.101382	0.63	-	-	1.28	-	0.42
TNF: (TNF OR TNFSF2	Hs.211600	-	-	-	-	-	1.42
TNFAIP2: (TNFAIP2) T	Hs.407546	-	0.48	-	-	0.89	1.16

Gen Name	UniGene	2828	3204	3230	2060	2810	3026
TNFAIP3: (TNFAIP3 OR	Hs.36	0.90	-	-	-	1.95	0.97
TNFAIP6: (TNFAIP6 OR	Hs.376208	1.12	-	-	2.41	1.28	1.28
TNFB: (LTA OR TNFSF1	Hs.159	0.82	1.42	-	1.47	1.29	1.24
TNFC: (LTB OR TNFC O	Hs.204044	0.33	-	-	3.15	0.38	1.26
TNFR1: (TNFRSF1A OR	Hs.81791	2.24	-	-	1.46	0.99	1.70
TNFRSF11A: (TNFRSF11	Hs.434975	0.92	0.85	-	1.90	1.13	0.85
TNFRSF11B: (TNFRSF11	Hs.256278	0.80	0.63	-	0.65	0.69	1.63
TNFRSF19L: (TNFRSF19	Hs.299558	1.40	0.79	-	1.54	0.98	2.94
TNFRSF1B: (TNFRSF1B	Hs.504816	-	-	-	-	-	0.91
TNFRSF5: (TNFRSF5 OR	Hs.82359	0.77	-	-	1.28	0.81	-
TNFRSF6: (TNFRSF6 OR	Hs.355307	0.51	0.75	-	1.69	0.98	1.12
TNFRSF7: (TNFRSF7 OR	Hs.1314	1.98	-	-	4.76	0.97	2.28
TNFRSF8: (TNFRSF8 OR	Hs.193418	1.36	0.75	-	1.68	1.37	1.28
TNFRSF9: (TNFRSF9 OR	Hs.333791	1.36	0.99	0.55	1.49	1.47	0.90
TNFSF11: (TNFSF11 OR	-	0.91	1.20	0.72	-	-	0.99
TNFSF12: (TNFSF12 OR	Hs.181097	1.38	1.73	-	1.23	0.90	1.18
TNFSF4: (TNFSF4 OR T	Hs.652	-	-	-	0.67	0.93	1.90
TNFSF5: (TNFSF5 OR C	Hs.2007	1.32	-	-	-	-	0.49
TNFSF6: (TNFSF6 OR F	Hs.99899	0.93	-	-	-	0.92	1.32
TNFSF7: (TNFSF7 OR C	Hs.177136	1.25	0.44	-	1.45	1.38	1.53
TNFSF8: (TNFSF8 OR C	Hs.1524	-	0.75	-	-	-	1.00
TNFSF9: (TNFSF9 OR L	Hs.440968	1.19	0.60	-	1.94	1.19	0.88
TP53BP1: (TP53BP1) T	Hs.274404	2.00	-	-	0.86	1.19	1.17
TPA: (PLAT) TISSUE-T	Hs.429961	0.49	0.86	-	0.22	0.33	0.89
TPARL: (TPARL) TRANS	Hs.89862	1.25	0.71	-	0.47	0.82	0.58
TRADD: (TRADD) TUMOR	Hs.438253	5.80	-	-	3.45	2.12	0.86
TRAF1: (TRAF1 OR EBI	Hs.437575	-	0.71	0.23	-	0.89	5.87
TRAF2: (TRAF2 OR TRA	Hs.297660	1.26	-	-	1.12	1.32	0.87
TRAF3: (TRAF3 OR CRA	Hs.8375	0.99	1.00	0.66	1.65	1.19	0.92
TRAF4: (TRAF4 OR MLN	Hs.385685	0.90	-	-	0.63	1.66	0.96
TRAF5: (TRAF5) (TNF	Hs.444172	1.55	0.53	-	0.64	1.14	0.98
TRAF6: (TRAF6) PUTAT	Hs.387871	0.88	0.59	-	0.98	1.19	0.83
TRAIL: (TNFSF1 OR T	Hs.401745	0.34	0.89	-	1.75	2.13	0.96
TRAILR1_HUMAN: (TRAI	Hs.51233	0.86	0.80	-	-	-	2.32
TRAILR2: (TRAILR2 OR	Hs.119684	1.14	-	-	1.35	1.64	0.88
TRAILR3_HUMAN: (TNFR	Hs.129844	1.69	1.42	-	1.24	1.33	0.95
TRAILR4_HUMAN: (TNFR	Hs.334174	-	1.59	0.53	-	-	2.98
TRAIN: (TNFRSF19 OR	Hs.21254	-	-	-	1.21	-	1.45
TTRAP: (TTRAP OR DJ3	Hs.210628	0.46	1.17	-	0.27	0.69	0.95
TUBA_HUMAN: (TUBA1)	Hs.446608 Hs.433394 Hs.406578	4.45	-	-	1.55	2.62	0.62
TUBB1-TUBB5_HUMAN: (	Hs.356729	3.85	1.52	0.81	0.53	1.15	1.43
UBE2G1: (UBE2G1 OR U	Hs.121150	0.72	1.48	-	0.74	1.17	0.81
UBIQUITIN_BAD: ((UBA	Hs.78563	0.55	-	-	0.55	1.87	0.97
UPA: (PLAU) UROKINAS	Hs.356190 Hs.183704	2.88	0.52	0.61	0.99	0.93	2.72
USP2: (USP2 OR UBP41	Hs.77274	0.87	0.95	-	1.32	1.26	1.60
UVRAG: (UVRAG OR UVR	Hs.125902	1.16	-	-	1.24	0.89	1.31
V7: (V7) LEUKOCYTE S	Hs.13137	0.93	-	-	0.49	0.89	1.43
VAV: (VAV) VAV PROTO	Hs.74115	1.00	-	-	1.44	-	1.43
VAV2: (VAV2) VAV2 PR	Hs.116237	-	0.63	0.47	-	-	0.99
VAV3: (VAV3) VAV-3 P	Hs.4248	1.76	-	-	1.44	0.85	1.43
VCAM1: (VCAM1 OR L1C	Hs.267659	0.79	-	-	0.68	1.42	1.16
VEGC: (VEGFC) VASCUL	Hs.109225	-	-	-	-	-	1.25
VEGF_1: (VEGF OR VEG	Hs.79141	0.80	-	-	1.58	-	1.13
VEGFB: (VEGFB OR VRF	Hs.73793	1.86	-	-	0.47	1.11	1.33
VEGFD: (FIGF OR VEGF	Hs.78781	-	-	-	1.72	-	0.51
VERSICAN: (CSPG2) VE	Hs.11392	2.43	-	-	11.15	-	1.16
VGR2: (KDR OR FLK1)	Hs.12337	-	-	-	-	-	0.84
VWF: (F8VWF OR VWF)	Hs.440848	0.83	-	-	-	-	1.19
WISP3: (WISP3 OR CCN	Hs.194678	-	-	-	-	1.86	3.32
WSB-1: (SWIP1 OR WSB	Hs.315379	1.20	-	-	1.61	0.75	1.29
WSB-2: (WSB2 OR SWIP	Hs.459470	1.59	1.17	-	1.23	1.26	0.97
XBP1: (XBP1 OR XBP2	Hs.437638	0.68	0.34	-	2.72	0.64	0.88
XIRAPL2: (IL1RAPL-2	Hs.272354	0.97	0.58	-	0.45	1.34	0.93
XRCC: (XRCC1) DNA-RE	Hs.98493	1.25	0.68	-	0.56	1.67	0.94
YES: (YES1 OR YES) P	Hs.194148	0.95	0.59	-	0.23	1.61	1.13
YWHAE: (YWHAE) 14-3-	Hs.79474	0.45	0.38	0.29	0.26	1.22	1.95
YWHAZ: (YWHAZ) 14-3-	Hs.386834	1.98	0.63	-	1.28	0.73	1.26
YY1: (YY1) TRANSCRIP	Hs.388927	1.98	-	-	1.28	1.43	0.88
ZAKI-4: (ZAKI-4 OR D	Hs.156007	0.33	-	-	-	0.68	1.12
ZAP7: (ZAP7 OR SRK	Hs.234569	-	-	-	-	-	1.14
ZF9: (COPEB OR KLF6	Hs.285313	0.82	0.74	0.65	0.50	0.78	1.20
ZIC3: (ZIC3) ZINC FI	Hs.111227	-	-	-	-	-	0.96
ZMDA1: (IL19 OR ZMDA	Hs.71979	0.77	0.99	-	1.15	1.28	1.38
ZNFN1A1: (ZNFN1A1 OR	Hs.435949	0.88	-	-	1.38	0.87	1.73

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Curriculum Vitae

Name: **Julia Diegmann**
Date of Birth: 20th of February 1977
Place of Birth: Fulda

e-mail: julia.diegmann@med.uni-muenchen.de

EDUCATION

1987–1996	Marienschule Fulda, Secondary School (Gymnasium), Fulda, Germany.
1996–1997	Volunteer. Social Year (FSJ), Sigüenza, Spain.
1997-1999	Spanish. Philipps University, Marburg, Germany.
1997-1999	Biology. Philipps University, Marburg, Germany.
1999-2000	Biology. University Alcalá de Henares, Henares, Spain.
2001-2002	Research Internship. Institute of Anthropology, Giessen, Germany.
2000-2002	Diplom (Msc). Biology. Justus-Liebig University, Giessen, Germany. *Advisor*: Prof. Dr. Manfred Kunter.
2004	Research Internship. Institute of Toxicology, Merck KGaA, Darmstadt, Germany.
2002-2006	Ph.D. Student. Friedrich-Schiller University, Jena, Germany. *Advisor*: PD. Dr. Ferdinand von Eggeling.
10.2006	Post-Doctoral Researcher. Ludwig-Maximilians University, Munich. Germany. Institute for Medical Psychology, Department Chronobiology

(Julia Diegmann)

Erklärung

Ich erkläre, dass mir die geltende Promotionsordnung der Fakultät bekannt ist.
Ich erkläre, dass ich die vorliegende Arbeit selbstständig und nur unter Verwendung der angegebenen Hilfsmitteln und Literatur angefertigt habe.
Ich erkläre, dass ich mich mit der vorliegenden Arbeit an keiner anderen Hochschule um den akademischen Grad Dr. rer. nat. beworben habe und dass ich weder früher noch gegenwärtig die Eröffnung eines Verfahrens zum Erwerb des oben genannten akademischen Grades an einer anderen Hochschule beantragt habe.

I hereby declare that this submission is my own work and that I used only the declared materials and literature stated.
I further declare that this thesis, in substantially its present form, has not been submitted or accepted previously for the award of a doctoral degree (Dr. rer. nat) in this or any other tertiary institution.

_____ _____
(Datum/Date) (Julia Diegmann)